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Moriarty(10) **Patent No.:** **US 9,150,584 B2**
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ISOQUINUCLIDENE DERIVATIVES AND
PROCESSES FOR PREPARING THEM**(71) Applicant: **DemeRx, Inc.**, Miami, FL (US)(72) Inventor: **Robert M. Moriarty**, Michiana Shores,
IN (US)(73) Assignee: **DEMEX, INC.**, Miami, FL (US)(*) Notice: Subject to any disclaimer, the term of this
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See application file for complete search history.

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Primary Examiner — Brenda Coleman(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP(57) **ABSTRACT**

Provided herein are indole and benzofuran fused isoquinu-
clidene derivatives. Also provided herein are processes, pref-
erably enantioselective processes, for preparing such deriva-
tives including processes for preparing (-) and (+)
noribogaine or a salt thereof, in substantially enantiomeri-
cally pure forms.

7 Claims, 3 Drawing Sheets

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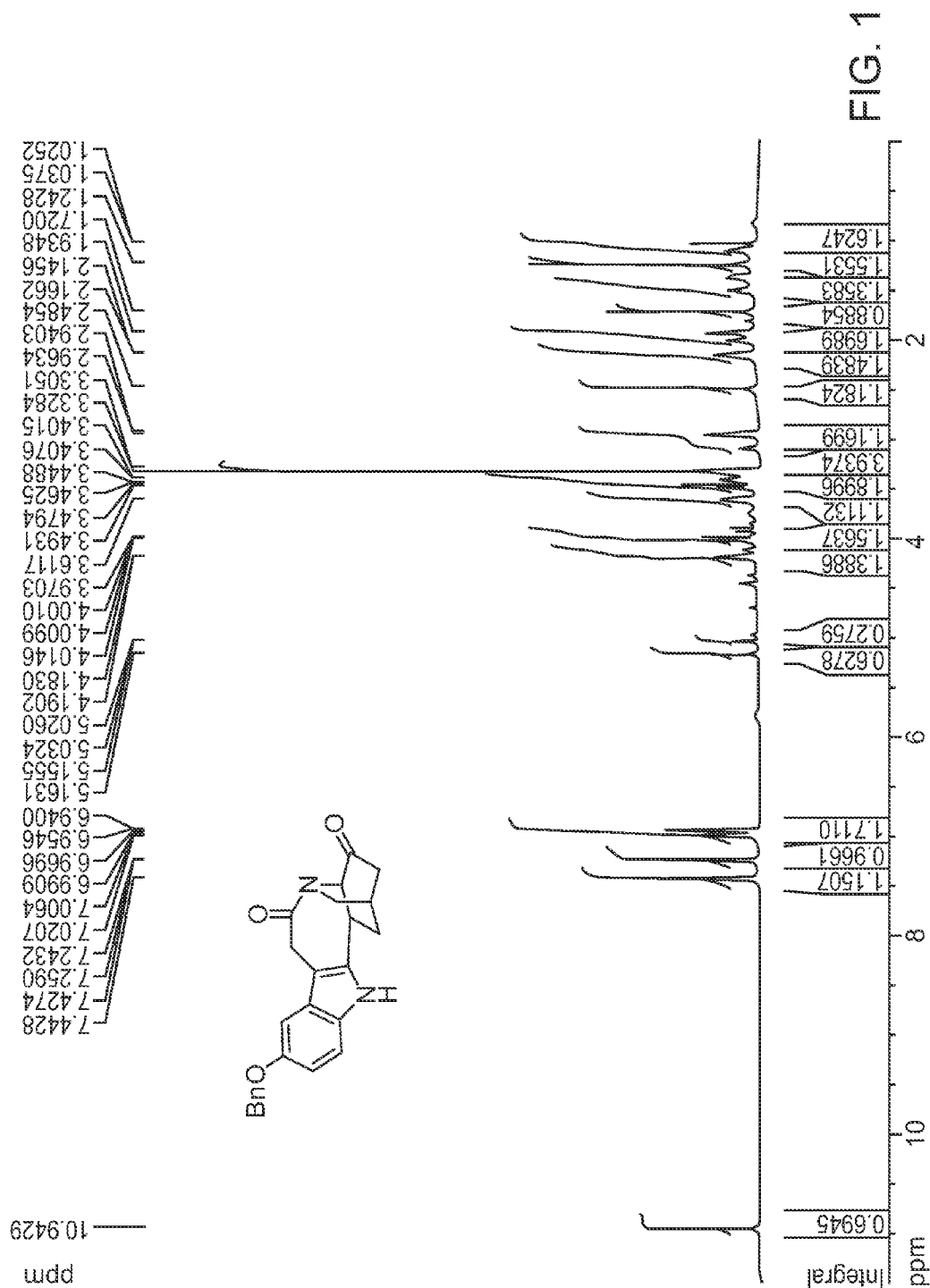
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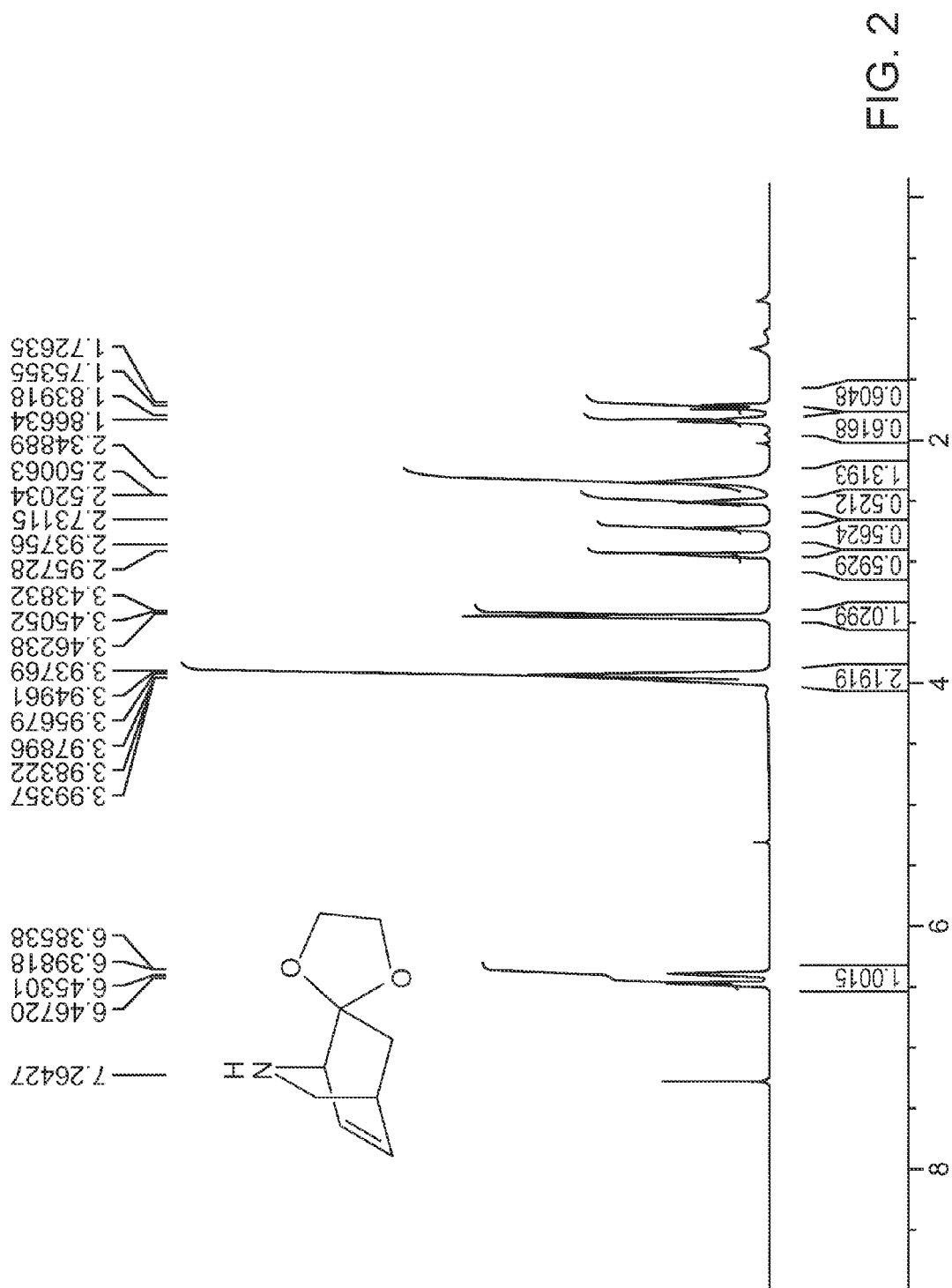
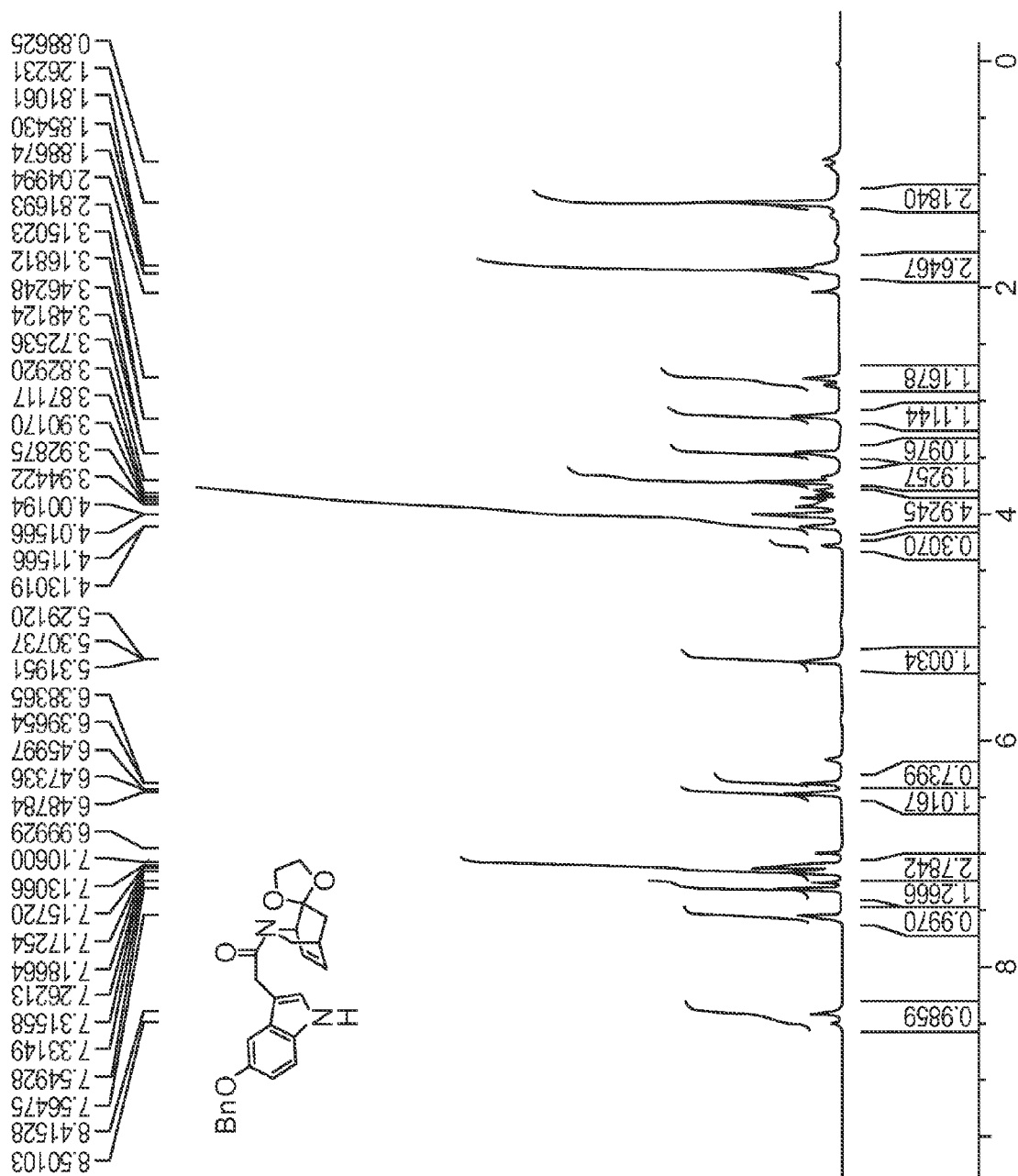


FIG. 3



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INDOLE AND BENZOFURAN FUSED ISOQUINUCLIDENE DERIVATIVES AND PROCESSES FOR PREPARING THEM

CROSS REFERENCE TO RELATED APPLICATION

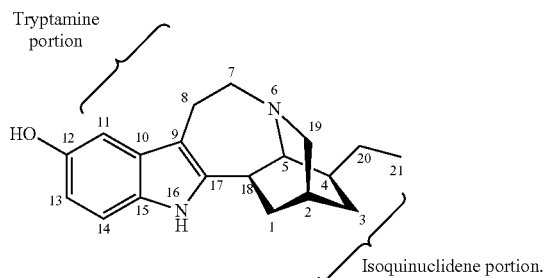
This application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application Ser. Nos. 61/590,740 filed Jan. 25, 2012 and 61/591,258 filed Jan. 26, 2012 and each of which is hereby incorporated by reference into this application in its entirety.

FIELD OF THE INVENTION

Provided herein are indole and benzofuran fused isoquinuclidene derivatives, and processes, preferably enantioselective processes, for preparing such derivatives including processes for preparing (–) and (+) noribogaine, in substantially enantiomerically pure forms. In certain aspects, the processes provided herein employ the novel isoquinuclidene, R,R 7-oxo-2-azabicyclo[2.2.2]oct-5-ene, or a protected derivative thereof (see, U.S. application No. 61/741,798, which is incorporated herein in its entirety by reference). In other aspects, this invention provides (–) or (+) noribogaine or a salt, preferably a pharmaceutically acceptable salt, of each thereof, preferably in a substantially enantiomerically pure form, prepared according to the processes provided herein, and also provides pharmaceutical compositions comprising (–) noribogaine or a salt thereof thus prepared.

STATE OF THE ART

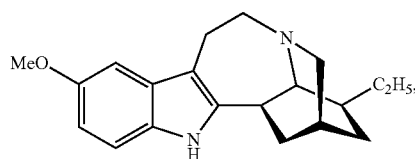
Noribogaine is a well known compound whose structure combines the features, for example, of tryptamine, and isoquinuclidene. The naturally occurring enantiomer of noribogaine can be depicted by the following formula:



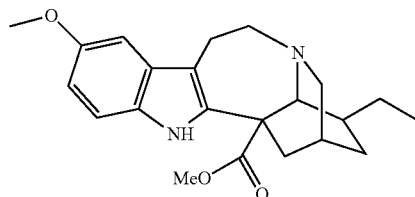
This enantiomer of noribogaine and its pharmaceutically acceptable salts have recently received significant attention as a non-addictive alkaloid useful in treating drug dependency (U.S. Pat. No. 6,348,456) and as a potent analgesic (U.S. Pat. No. 7,220,737). Both of these patents are incorporated herein by reference in their entirety.

Synthesizing compounds to include the isoquinuclidene moiety, especially in a substantially enantiomerically pure form is a challenging task. Heretofore, Iboga alkaloids, such as ibogaine:

2



were conventionally prepared from one of its naturally occurring precursors such as voacangine:



or isolated from plant sources. The naturally occurring enantiomer of noribogaine is prepared by O-demethylation of naturally occurring ibogaine or prepared by decarboxylation and O-demethylation of naturally occurring voacangine. Voacangine and Ibogaine are obtained from plants where both the supply is limited and the quality of the supply is unpredictable.

SUMMARY OF THE INVENTION

Provided herein are indole and benzofuran fused isoquinuclidene derivatives, and processes, preferably enantioselective processes, for preparing such derivatives including processes for preparing (–) or (+) noribogaine or a salt thereof, in substantially enantiomerically pure forms.

In certain aspects, the processes provided herein employ the novel 1R,4R 7-oxo-2-azabicyclo[2.2.2]oct-5-ene or a protected derivative thereof.

In another aspect, this invention provides (–) noribogaine or a salt, preferably a pharmaceutically acceptable salt, thereof, preferably in a substantially enantiomerically pure form, prepared according to the processes provided herein. In another aspect, this invention provides a composition comprising the (–) noribogaine or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

This invention also provides processes for preparing (+) noribogaine.

As used herein, “pharmaceutically acceptable” refers to a safe and non-toxic composition, which is suitable for in vivo, preferably for human administration. Pharmaceutically acceptable salts or excipients are well known to the skilled artisan.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 illustrates a ¹H-NMR spectrum in CDCl₃ of compound 3:

3

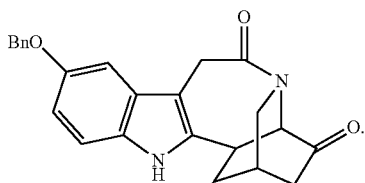


FIG. 2 illustrates a ^1H -NMR spectrum in CDCl_3 of compound 1:

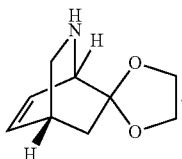
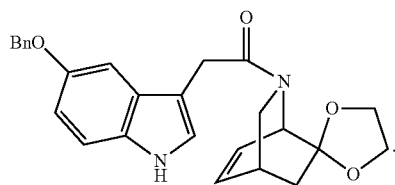


FIG. 3 illustrates a ^1H -NMR spectrum in CDCl_3 of compound 2:



DETAILED DESCRIPTION OF THE INVENTION

Provided herein are indole and benzofuran fused isoquinolidene derivatives, and processes, preferably enantioselective processes, for preparing such derivatives including processes for preparing (–) and (+) noribogaine or a salt of each thereof, in substantially enantiomerically pure forms. Before this invention is described in greater detail, the following terms will be defined.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a salt” includes a plurality of such salts.

DEFINITIONS

As used herein, “alkenyl” refers to hydrocarbyl groups having from 2 to 10 carbon atoms and at least one and up to 3 carbon carbon double bonds. Examples of alkenyl include vinyl, allyl, dimethyl allyl, and the like.

As used herein, “alkoxy” refers to —O-alkyl.

As used herein, “alkyl” refers to hydrocarbyl groups having from 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms, and still more preferably 1-4 carbon atoms. The alkyl group may contain linear or branched carbon chains. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, n-decyl and the like.

As used herein, “alkynyl” refers to hydrocarbyl groups having from 2 to 10 carbon atoms and at least one and up to 2

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carbon carbon triple bonds. Examples of alkynyl include ethynyl, propargyl, dimethylpropargyl, and the like.

As used herein, “amino” refers to —NR^xR^y wherein each R^x and R^y independently is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₂-C₁₀ heteroaryl, or C₃-C₈ heterocyclyl, or R^x and R^y together with the nitrogen atom they are bonded to form a 5-10 membered heterocyclyl ring containing 1-2 nitrogen and/or oxygen atoms, which heterocyclyl ring is optionally substituted with 1-3, preferably, 1-2, or more preferably, a single, C₁-C₃ alkyl group.

As used herein, “aryl” refers to an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom.

As used herein, “base” refers to a compound that can accept a proton or donate a lone electron pair. Examples of bases include, alkali (OH), carbonate, bicarbonate, alkoxides (alkyl-O[–]), hydrides (alkali metal hydrides and CaH₂), amides (NH₂[–], R^bNH[–], or (R^b)₂N[–]), wherein R^b is alkyl or 2 R^bs together with the nitrogen form a 5-6 membered ring), and neutral nitrogen containing bases such as (R^b)₃N, pyridine, 4-N,N-dialkylpyridine, and the like. As used herein nucleophilic bases refer to preferably neutral nitrogen containing bases that can catalyze the addition of an acyl halide or a sulfonyl halide (such as R^bCOX or R^bSO₂X) to an —OH, —NH₂, or an —NHR^b group. Preferred examples include, 4-N,N-dialkylpyridines.

As used herein, a “Bronsted acid” refers to a compound that can donate a proton.

As used herein, the term “chlorinated solvent” refers to chlorinated methane and ethane, which are preferably trichlorinated, and more preferably dichlorinated. Yet more preferably, the chlorinated solvent is dichloromethane.

As used herein, the term “comprising” or “comprises” is intended to mean that the compositions and methods include the recited elements, but not excluding others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. “Consisting of” shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

As used herein, “cycloalkyl” refers to cyclic hydrocarbyl groups of from 3 to 10 carbon atoms having single or multiple condensed rings, which condensed rings may be aromatic or contain a heteroatom, provided that the point of attachment is at a cycloalkyl carbon atom. Cycloalkyl includes, by way of example, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl and the like. Cycloalkyl rings are preferably saturated, though, cycloalkyl rings including 1-2 carbon carbon double bonds are also contemplated provided that the ring is not aromatic.

As used herein, “C” refers to a group having x carbon atoms, wherein x is an integer, for example, C₄ alkyl refers to an alkyl group having 4 carbon atoms.

As used herein, “ee” refers to enantiomeric excess and is expressed as (e¹–e²) % where e¹ and e² are the two enantiomers. For example, if the % of e¹ is 95 and the % of e² is 5, then the e¹ enantiomer is present in an ee of 90%. The ee of an

enantiomer in a mixture of enantiomers is determined following various methods well known to the skilled artisan, such as using chiral lanthanide based nuclear magnetic resonance shift reagents, forming derivatives with chiral compounds such as chiral hydroxyacids, amino acids, and the like. Various physical measurements such as circular dichroism, optical rotation, etc. are also useful in determining the ee of a mixture of enantiomers.

As used herein, "deprotection condition" refers to reaction conditions that transform a phenolic ether to the corresponding phenol and includes reacting with various Lewis acids such as BBr_3 , and when the alkyl group in the ether is a methyl group containing at least one phenyl or substituted phenyl group, reacting under hydrogenation conditions.

As used herein, $-\text{CO}_2\text{H}$ "ester" refers to $-\text{CO}_2\text{R}^E$ wherein R^E is selected from the group consisting of $\text{C}_6\text{-C}_{10}$ aryl and $\text{C}_1\text{-C}_6$ alkyl optionally substituted with 1-3 $\text{C}_6\text{-C}_{10}$ aryl groups.

As used herein "Fischer indole synthesis condition" refers to reaction conditions for reacting phenylhydrazine with a ketone containing at least one α -methylene group and an acid to provide an indole derivative. Bronsted acids such as HCl , H_2SO_4 , polyphosphoric acid and p-toluenesulfonic acid are useful, as are Lewis acids such as boron trifluoride, zinc chloride, iron chloride, and aluminum chloride.

As used herein, "fluoroalkyl" refers to an alkyl group substituted with up to 5, or preferably up to 3 fluoro groups.

As used herein, "halo" refers to F, Cl, Br, or I.

As used herein, "heteroaryl" refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur within the ring, wherein the nitrogen and/or sulfur atom(s) of the heteroaryl are optionally oxidized (e.g., N-oxide, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$), provided that the ring has at least 5 ring atoms and up to 14, or preferably from 5-10, ring atoms. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizynyl or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. Examples of heteroaryls include pyridyl, pyrrolyl, indolyl, thiophenyl, furyl, and the like.

As used herein, "heterocyclyl" or heterocycle refers to a cycloalkyl group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur within the ring, wherein the nitrogen and/or sulfur atom(s) of the heteroaryl are optionally oxidized (e.g., N-oxide, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$), provided that the ring has at least 3 and up to 14, or preferably from 5-10 ring atoms. Such heterocyclyl groups can have a single ring or multiple condensed rings wherein the condensed rings may not contain a heteroatom and/or may contain an aryl or a heteroaryl moiety, provided that the point of attachment is through an atom of the non-aromatic heterocyclyl group. Examples of heterocyclyl include pyrrolidinyl, piperadinyl, piperazinyl, and the like. Heterocyclyl rings are preferably saturated, though, heterocyclyl rings including 1-2 carbon carbon double bonds are also contemplated provided that the ring is not aromatic.

As used herein, "hydrogenation conditions" refer to conditions including hydrogen gas at atmospheric or higher pressure and catalysts that catalyze the reaction of the hydrogen with a hydrogen reactive group, such as a benzyl group or a carbon carbon double/triple bond. Catalysts useful for hydrogenation include palladium, platinum, and rhodium metals and their oxides or hydroxides, preferably supported on a material such as carbon or alumina.

As used herein, "protecting group" or "Pg" refers to well known functional groups which, when bound to a functional group, render the resulting protected functional group inert to the reaction to be conducted on other portions of the compound and the corresponding reaction condition, and which can be reacted to regenerate the original functionality under deprotection conditions. The protecting group is selected to be compatible with the remainder of the molecule. In one embodiment, the protecting group is an "amine protecting group" which protects an $-\text{NH}-$ or an $-\text{NH}_2-$ moiety, for example during the syntheses described here. Examples of amine protecting groups include, for instance, benzyl, acetyl, oxyacetyl, carbonyloxybenzyl (Cbz), Fmoc, and the like. In another embodiment, the protecting group is a "hydroxy protecting group" which protects a hydroxyl functionality during the synthesis described here. Examples of hydroxyl protecting groups include, for instance, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, dialkylsilyl ethers, such as dimethylsilyl ether, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, and t-butyl dimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates such as methyl, ethyl, 2,2,2-trichloroethyl, allyl, and benzyl. As the skilled artisan would appreciate, one or more of these protecting groups are also useful as amine protecting groups. Additional examples of amine, hydroxy, and keto protecting groups are found in standard reference works such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 2d Ed., 1991, John Wiley & Sons, and McOmie *Protective Groups in Organic Chemistry*, 1975, Plenum Press. Methods for protecting and deprotecting hydroxyl, $-\text{NH}-$, $-\text{NH}_2-$, and keto groups disclosed herein can be found in the art, and specifically in Greene and Wuts, *supra*, and the references cited therein.

As used herein, a "Lewis acid" refers to a compound that can donate a lone electron pair.

As used herein, a "non nucleophilic base" refers to a base that is capable of abstracting an acidic hydrogen, e.g., from an $-\text{OH}$ or $-\text{NH}-$ moiety, but does not readily take part in a nucleophilic substitution reaction. Preferably such bases are metal hydrides such as alkali metal hydrides or CaH_2 .

As used herein, "oxidizing agent" refers to a compound that can accept electrons, and e.g., convert a $\text{CH}(\text{OH})$ group to a keto group. Examples of oxidizing agents are well known, and non limiting examples include hexavalent chromium reagents such as pyridinium chlorochromate, pyridinium dichromate, hypervalent iodine, and hypochlorite.

As used herein, "reducing agent" refers to a compounds that can donate electrons or a hydride in a reaction. Preferred examples include borohydrides such as $\text{NaBH}_4/\text{CeCl}_3$, and alanes such as diisobutyl aluminum hydride.

As used herein, a salt refers to preferably a salt of a mineral acid, or an organic acid such as a carboxylic acid or a sulfonic acid, and/or to alkali, alkaline earth, and various ammonium (including tetraalkyl ammonium, pyridinium, imidazolium and the like) salts. Non limiting examples of acid salts include salts of hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methane sulfonic acid, phosphorous acid, nitric acid, perchloric acid, acetic acid, tartaric acid, lactic acid, succinic acid, and citric acid.

As used herein, the term " $((S)\text{-binol})$ " refers to the (S)-enantiomer of 1,1'-bi-2-naphthol, and " $((R)\text{-binol})$ " refers to the (R)-enantiomer of 1,1'-bi-2-naphthol.

As used herein, "silyl" refers to $\text{Si}(\text{R}')_3$ wherein each R' independently is $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_6\text{-C}_{10}$ aryl.

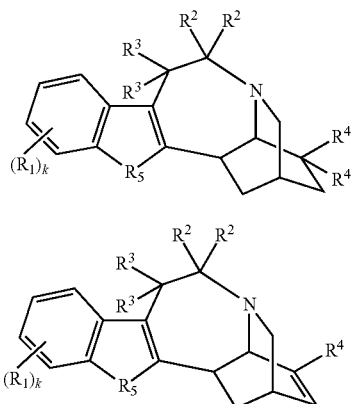
As used herein, "substantially enantiomerically enriched," "substantially enantiomerically pure" or "substantial enan-

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tiomeric excess” or grammatical equivalents thereof refers to an enantiomer in an enantiomeric mixture with at least 95% ee, preferably 98% ee, or more preferably 99% ee.

Compounds of the Invention

In one aspect, this invention provides compounds of Formulas (I) and (VI):



or a salt or enantiomer thereof wherein

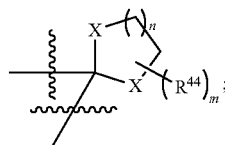
k is 1, 2, or 3;

each R^1 is independently selected from the group consisting of hydrogen, halo, amino, hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof, wherein the alkyl, alkoxy, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy, and $-CO_2H$ or an ester thereof;

R^2 is hydrogen or $C(R^2)_2$ is a keto group;

R^3 is selected from the group consisting of hydrogen, halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof;

each R^4 independently is selected from the group consisting of hydrogen, hydroxy, $-SR^{41}$, $-OR^{42}$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, and C_2 - C_6 alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, C_1 - C_6 alkoxy, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof, or the 2 R^4 groups together with the carbon atom to which they are bonded to form a keto ($C=O$) group, a Schiff base ($=NR^{43}$), a vinylidene moiety of formula $=CR^{48}R^{49}$, or form a cyclic ketal or thioketal, which cyclic ketal or thioketal is of formula:



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each R^{41} is independently selected from the group consisting of C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, C_3 - C_8 heterocyclyl, halo, amino, $-N_3$, hydroxy, C_1 - C_6 alkoxy, silyl, nitro, cyano, and CO_2H or an ester thereof, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_6 - C_{10} aryl, C_2 - C_{10} heteroaryl, C_3 - C_8 cycloalkyl, and C_3 - C_8 heterocyclyl;

each R^{42} is independently selected from the group consisting of C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of C_6 - C_{10} aryl, C_3 - C_8 cycloalkyl, C_2 - C_{10} heteroaryl, C_3 - C_8 heterocyclyl, halo, amino, $-N_3$, hydroxy, C_1 - C_6 alkoxy, silyl, nitro, cyano, and CO_2H or an ester thereof, C_2 - C_6 alkenyl, and C_2 - C_6 alkynyl;

where X in both occurrences is either oxygen or sulfur;

m is 1, 2, 3, or 4;

n is 1 or 2;

R^{43} is selected from the group consisting of C_6 - C_{10} aryl and C_2 - C_{10} heteroaryl;

R^{44} is selected from the group consisting of C_1 - C_6 alkyl and C_6 - C_{10} aryl;

R^{48} is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, and C_2 - C_6 alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, C_1 - C_6 alkoxy, amino, hydroxy, cyano, nitro, $-N_3$, $-NHCOCH_3$, and $-CO_2H$ or an ester thereof;

R^{49} is hydrogen or C_1 - C_6 alkyl;

R^5 is selected from the group consisting of $-O-$ and $N-R^{51}$; and

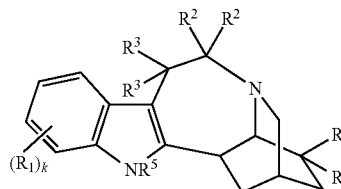
R^{51} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, $-N_3$, and $-CO_2H$ or an ester thereof;

wherein the C^{14} content of a compound of Formula (I), that is tabernanthine, ibogamine, ibogaline, ibogamine, and noribogaine is less than 0.9 ppt, preferably less than 0.8 ppt, or more preferably less than 0.8 ppt.

A keto substituent, as used herein, substitutes a $-CH_2-$ group to a $-C(=O)-$ group. In one embodiment, the compound of Formula (I) excludes a compound selected from Iboga alkaloids. As used herein, Iboga alkaloids are alkaloids, isolated from the plant Tabernanthe Iboga that contain a tryptamine and an isoquinuclidene moiety as present in ibogaine or noribogaine. In one embodiment, the excluded iboga alkaloid is tabernanthine, ibogamine, ibogaline, ibogamine, or noribogaine.

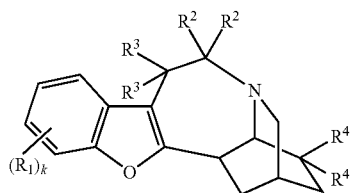
In one embodiment, the compound of Formula (I) is of Formula (IA) or (IB):

(IA)



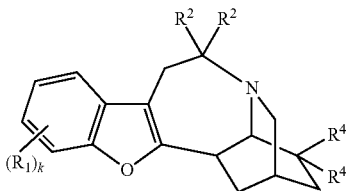
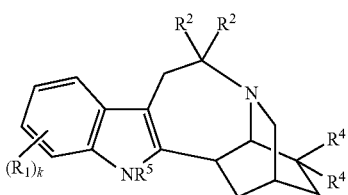
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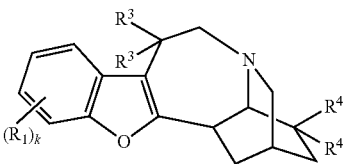
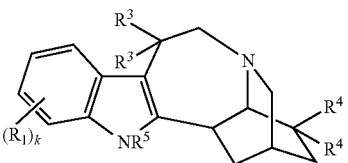
wherein k and R^1 , R^2 , R^3 , R^4 , and R^5 are defined as in Formula (I) above.

In another embodiment, the compound of Formula (I) is of Formula (IIA) or (IIB):



wherein k and R^1 , R^2 , R^4 , and R^5 are defined as in Formula (I) above.

In another embodiment, the compound of Formula (I) is of Formula (IIIA) or (IIIB):



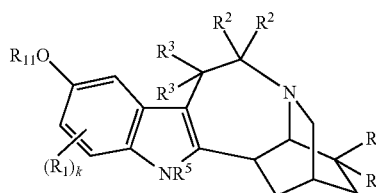
wherein k and R^1 , R^3 , R^4 , and R^5 are defined as in Formula (I) above.

In another embodiment, the compound of Formula (I) is of Formula (IVA) or (IVB):

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(IB)

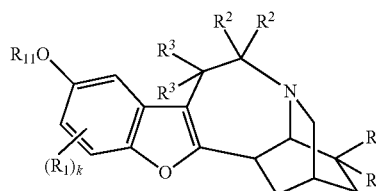
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(IVA)

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(IVB)

(IIA)

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wherein R^{11} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl optionally substituted with 1-3 substituents selected from the group consisting of halo, amino, hydroxy, cyano, nitro, $-N_3$, $-CO_2H$ or an ester thereof, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy;

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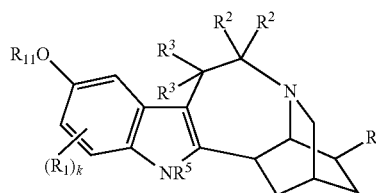
(IIB)

k is 1 or 2;
and R^1 , R^2 , R^3 , R^4 , and R^5 are defined as in Formula (I) above.

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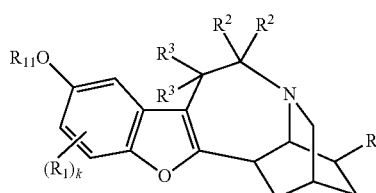
In another embodiment, the compound of Formula (I) is of Formula (IVC), (IVD), (VIA), or (VIB):

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(IVC)

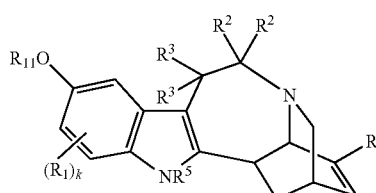
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(IVD)

(IIIA)

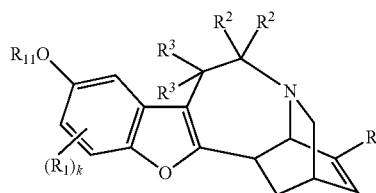
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(VIA)

(IIIB)

50



(VIB)

60

65

wherein R^{11} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl optionally substituted with 1-3 substituents

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ents selected from the group consisting of halo, amino, hydroxy, cyano, nitro, $-\text{N}_3$, and $-\text{CO}_2\text{H}$ or an ester thereof, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of C_1 - C_6 alkyl and C_1 - C_6 alkoxy;

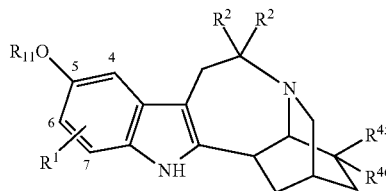
k is 1 or 2;

and R^1 , R^2 , R^3 , R^4 , and R^5 are defined as in Formula (I) above.

In another embodiment, the present invention provides compounds of formula (VA):

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(VA)



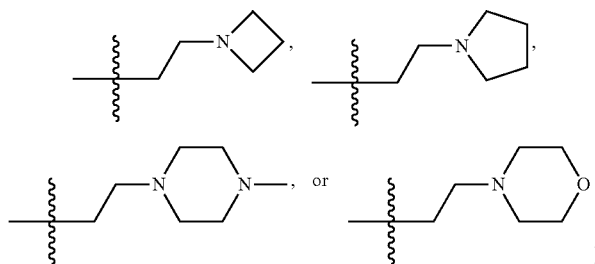
as tabulated below:

R^1	R^{11}	$\text{C}(\text{R}^2)_2$	R^{45}	R^{46}	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	$\text{C}=\text{O}$	$\text{CR}^{45}\text{CR}^{46}$ is $\text{C}=\text{O}$	—	—
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	$\text{C}=\text{O}$	$\text{CR}^{45}\text{CR}^{46}$ is $\text{C}=\text{CR}^{48}\text{H}$, R^{48} is Me, Et, Pr, Bu	—	—
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH_2	$\text{CR}^{45}\text{CR}^{46}$ is $\text{C}=\text{CR}^{48}\text{H}$, R^{48} is Me, Et, Pr, Bu	—	—

H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe

Bn $\text{C}=\text{O}$ $\text{CH}=\text{CHR}^{47}$ OH

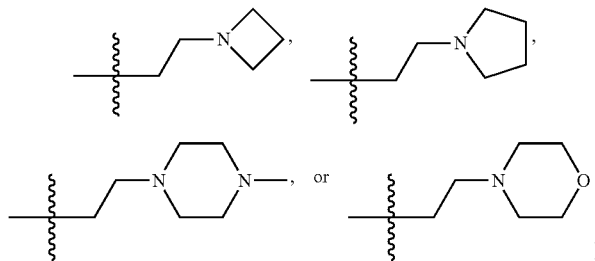
H or C_1 - C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe , $(\text{CH}_2)_2\text{OMe}$, $(\text{CH}_2)_3\text{OMe}$, and $(\text{CH}_2)_4\text{OMe}$), OH group (e.g., CH_2OH , $(\text{CH}_2)_2\text{OH}$, $(\text{CH}_2)_3\text{OH}$, and $(\text{CH}_2)_4\text{OH}$), an amide (e.g., $(\text{CH}_2)_2\text{NHCOMe}$, $(\text{CH}_2)_3\text{NHCOMe}$, and $(\text{CH}_2)_4\text{NHCCOMe}$) or with an amino group (e.g.,



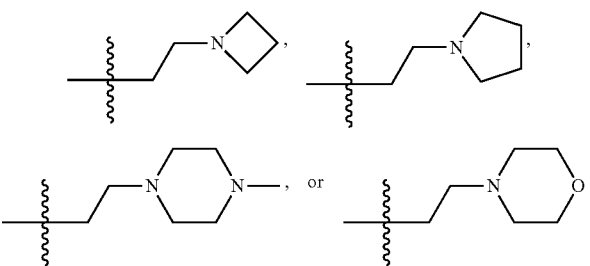
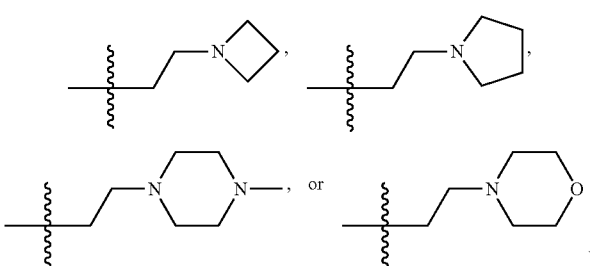
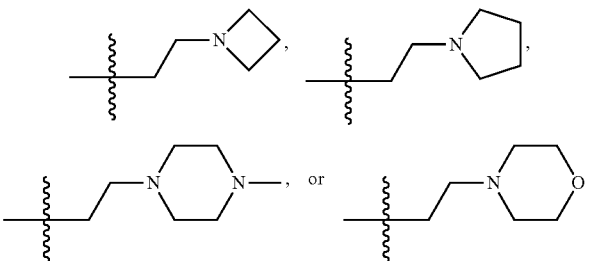
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe

Bn $\text{C}=\text{O}$ $\text{C}=\text{CR}^{47}$ OH

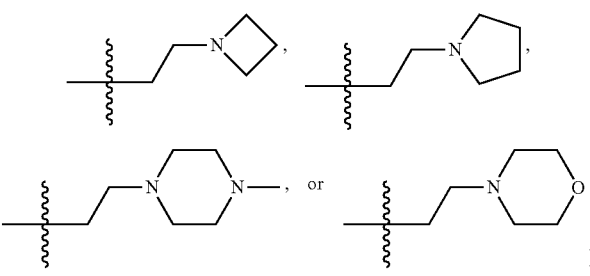
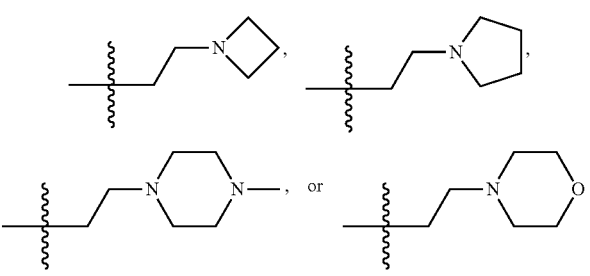
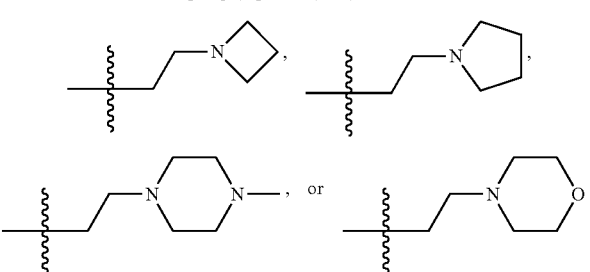
H or C_1 - C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe , $(\text{CH}_2)_2\text{OMe}$, $(\text{CH}_2)_3\text{OMe}$, and $(\text{CH}_2)_4\text{OMe}$), OH group (e.g., CH_2OH , $(\text{CH}_2)_2\text{OH}$, $(\text{CH}_2)_3\text{OH}$, and $(\text{CH}_2)_4\text{OH}$), an amide (e.g., $(\text{CH}_2)_2\text{NHCOMe}$, $(\text{CH}_2)_3\text{NHCOMe}$, and $(\text{CH}_2)_4\text{NHCCOMe}$) or with an amino group (e.g.,



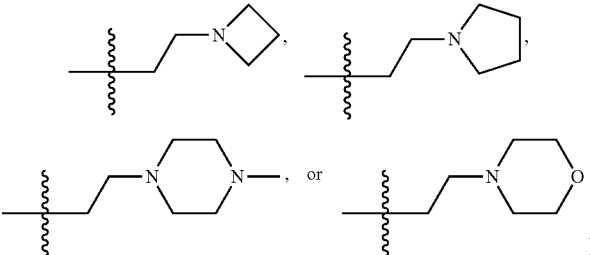
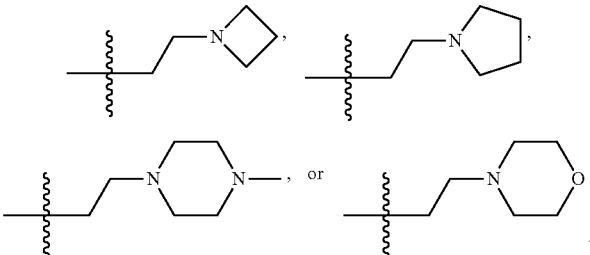
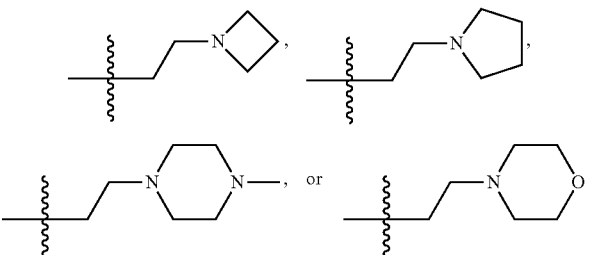
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R^1	R^{11}	$C(R^2)_2$	R^{45}	R^{46}	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	C=O	$CH_2CH_2R^{47}$	H	<p>C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g.,</p>  <p>)</p>
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	C=O	$CH_2CH_2R^{47}$	OH	<p>C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g.,</p>  <p>)</p>
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH ₂	CH=CHR ⁴⁷	OH	<p>H or C₁-C₄ alkyl (e.g., Me Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g.,</p>  <p>)</p>

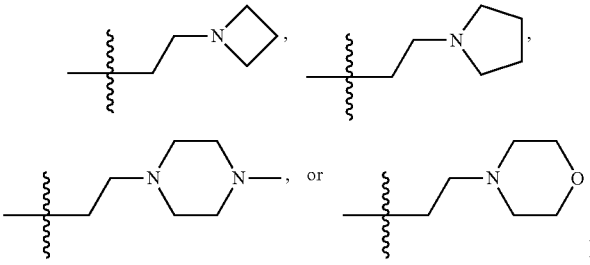
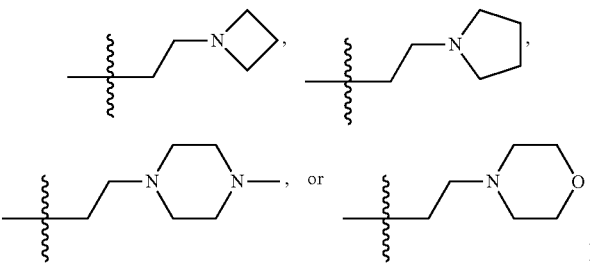
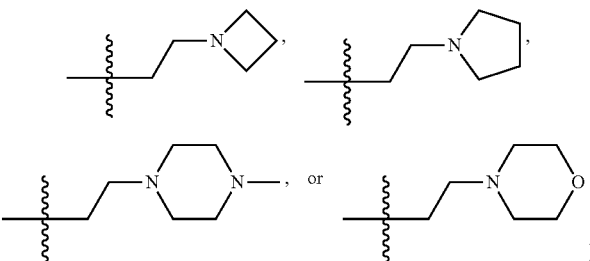
-continued

R^1	R^{11}	$C(R^2)_2$	R^{45}	R^{46}	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH_2	$C\equiv CR^{47}$	OH	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH_2	$CH_2CH_2R^{47}$	H	<p>C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH_2	$CH_2CH_2R^{47}$	OH	<p>C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 

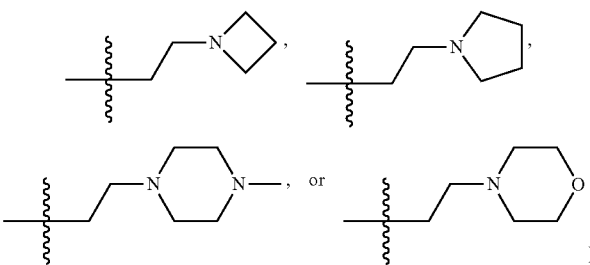
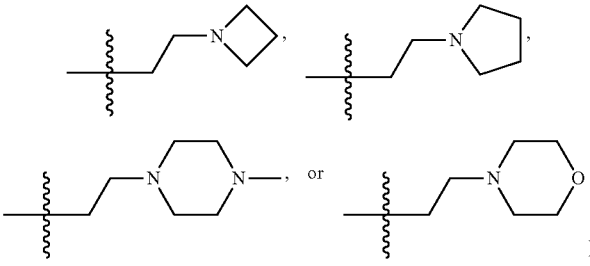
-continued

R^1	R^{11}	$C(R^2)_2$	R^{45}	R^{46}	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	$C=O$	$CH=CHR^{47}$	OH	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	$C=O$	$C\equiv CR^{47}$	OH	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	$C=O$	$CH_2CH_2R^{47}$	H	<p>C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 

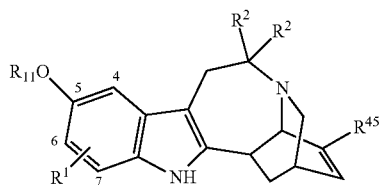
-continued

R^1	R^{11}	$C(R^2)_2$	R^{45}	R^{46}	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	$C=O$	$CH_2CH_2R^{47}$	OH	<p>C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	CH_2	$CH=CHR^{47}$	OH	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	CH_2	$C=CR^{47}$	OH	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 

-continued

R^1	R^{11}	$C(R^2)_2$	R^{45}	R^{46}	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	CH_2	$CH_2CH_2R^{47}$	H	<p>C_1-C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe, $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g., $CO_2(CH_2)_2NMe_2$,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	H	CH_2	$CH_2CH_2R^{47}$	OH	<p>C_1-C_4 alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH_2OMe, $(CH_2)_2OMe$, $(CH_2)_3OMe$, and $(CH_2)_4OMe$), OH group (e.g., CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, and $(CH_2)_4OH$), an amide (e.g., $(CH_2)_2NHCOMe$, $(CH_2)_3NHCOMe$, and $(CH_2)_4NHCCOMe$) or with an amino group (e.g., $CO_2(CH_2)_2NMe_2$,</p> 

In another embodiment, this invention provides a compound of Formula (VIC):

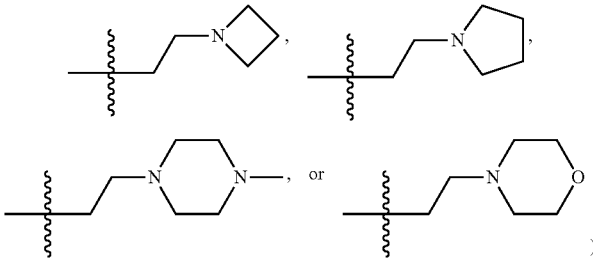
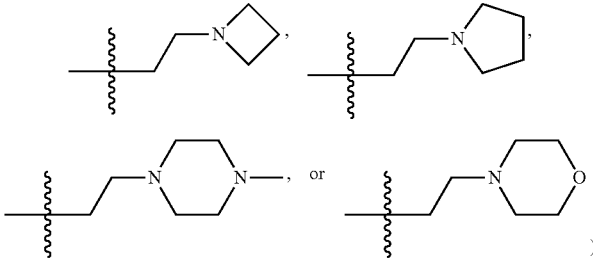
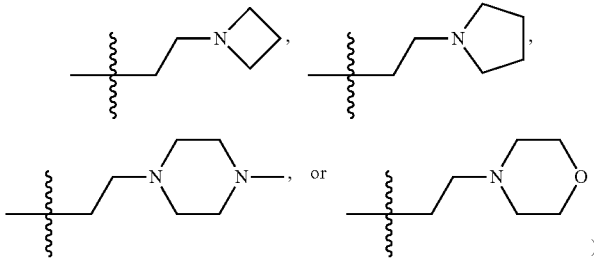


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(VIC)

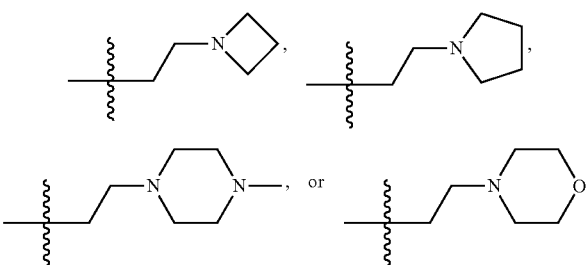
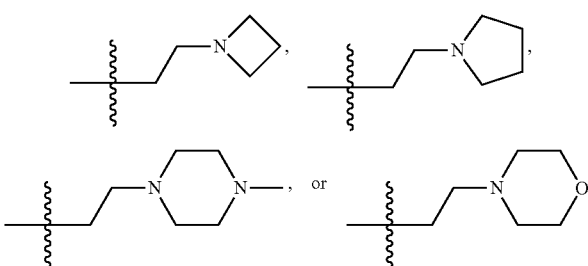
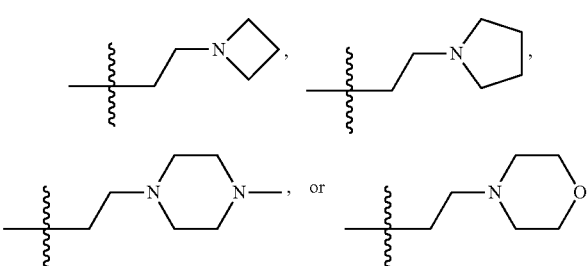
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as tabulated below:

R^1	R^{11}	$C(R^2)_2$	R^{45}	R^{47}
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	$C=O$	$CH=CHR^{47}$	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂),</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	$C=O$	$C\equiv CR^{47}$	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂),</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	$C=O$	$CH_2CH_2R^{47}$	<p>C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂),</p> 

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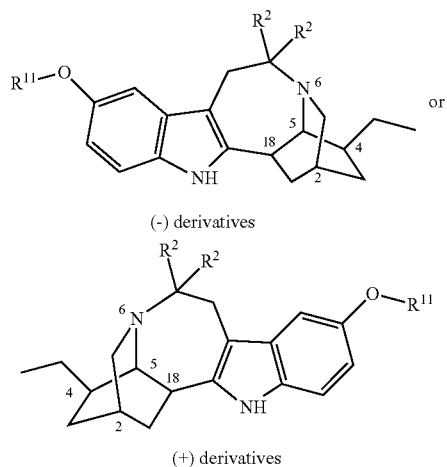
R ¹	R ¹¹	C(R ²) ₂	R ⁴⁵	R ⁴⁷
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH ₂	CH=CHR ⁴⁷	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH ₂	C=CR ⁴⁷	<p>H or C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 
H, 4-Me, 6-Me, 7-Me, 4-OH, 6-OH, 7-OH, 4-OMe, 6-OMe, or 7-OMe	Bn	CH ₂	CH ₂ CH ₂ R ⁴⁷	<p>C₁-C₄ alkyl (e.g., Me, Et, Pr, Bu) optionally substituted with an OMe group (e.g., CH₂OMe, (CH₂)₂OMe, (CH₂)₃OMe, and (CH₂)₄OMe), OH group (e.g., CH₂OH, (CH₂)₂OH, (CH₂)₃OH, and (CH₂)₄OH), an amide (e.g., (CH₂)₂NHCOMe, (CH₂)₃NHCOMe, and (CH₂)₄NHCCOMe) or with an amino group (e.g., CO₂(CH₂)₂NMe₂,</p> 

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As used herein, Me, Et, Pr, Bu and Bn, refer to methyl, ethyl, propyl, butyl, and benzyl, respectively.

In another embodiment, this invention provides an isolated enantiomer of a compound of any one of Formulas (I), (IA), (IB), (IIA), (IIB), (IIIA), (IIIB), (IVA), (IVB), (IVC), (IVD), (VA), (VI), (VIA), (VIB), or (VIC) in substantial enantiomeric excess.

In one embodiment, this invention provides a compound of formula:



in a substantially enantiomeric ally enriched form, or a salt of each thereof, wherein R^1 is C_1 - C_4 alkyl optionally substituted with a phenyl or a substituted phenyl group, wherein the substituted phenyl is substituted with 1-3 C_1 - C_4 alkyl or C_1 - C_4 alkoxy groups and R_2 is hydrogen or $C(R^2)_2$ is $C=O$.

In another embodiment, R_2 is hydrogen. In another embodiment, $C(R^2)_2$ is $C=O$. In another embodiment, R^1 is methyl or benzyl. In another embodiment, the compound is provided as an isolated enantiomer in substantial enantiomeric excess.

In another embodiment, this invention provides (+) noribogaine. In another embodiment, the (+) noribogaine has a ^{14}C content of less than 1 ppt, preferably less than 0.9 ppt, and more preferably less than 0.8 ppt.

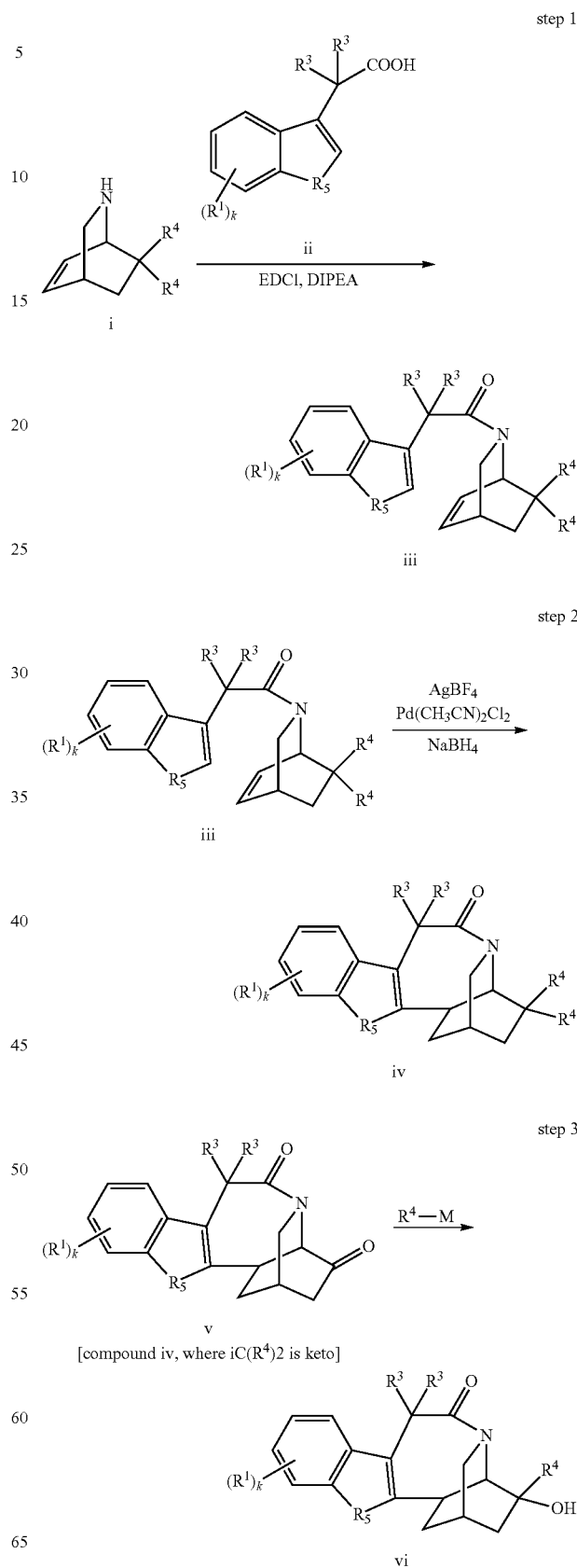
^{14}C has a half-life of about 5,730 years and is generated in the upper atmosphere as $^{14}CO_2$. The amount of $^{14}CO_2$ present is approximately 1 ppt (parts per trillion) and, through photosynthesis, accumulates in plants resulting in a ^{14}C content of plant material of approximately 1 ppt. Accordingly, plant derived compounds are expected to have approximately 1 ppt ^{14}C . Conversely, the synthetic compounds disclosed herein are derived from fossil fuels, which, due to ^{14}C decay, would have a ^{14}C content of less than 1 ppt ^{14}C . Accordingly, provided herein are synthetic indole and benzofuran fused isoquinclidene derivative having a ^{14}C content of less than 1 ppt, preferably, less than 0.90 ppt, or more preferably less than 0.8 ppt.

Processes of the Invention

Compounds of this invention are prepared as schematically illustrated below:

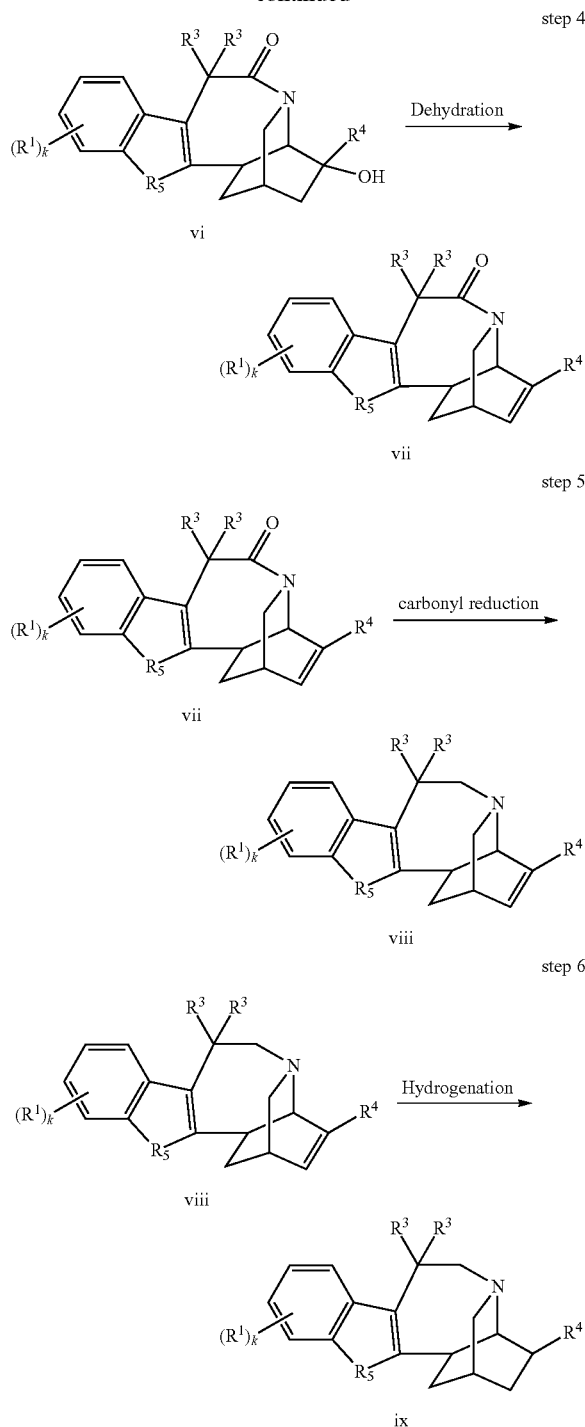
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Scheme 1



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-continued



In the scheme above, k , R^1 , R^2 , R^3 , and R^5 are defined as in any aspect or embodiment herein. Compound i is obtained, following the procedure described in U.S. application Ser. No. 13/358,446, which is incorporated herein in its entirety by reference. Compound ii is available commercially or prepared easily from commercially available material following steps well known in the art.

In one embodiment, this invention provides a process for preparing compound iii comprising contacting compound i with compound ii under conditions to provide compound iii. Accordingly, in step 1, compound i is coupled with com-

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pound ii, preferably in an inert solvent, in the presence of an amide or an ester coupling reagent. Various such coupling agents such as carbodiimides or (O-Benzotriazole- N,N,N' , N' -tetramethyl uronium hexafluorophosphate) HBTU or (2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate) HATU, and their immobilized derivatives are well known in the art and available commercially, for example, from Sigma-Aldrich Co. The reaction is carried out under suitable conditions to effect reaction completion. Typically, the reaction is carried out at 0-50° C. for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, 1H -nuclear magnetic resonance (NMR) spectroscopy, and the likes. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the products may be used for a subsequent reaction without further purification.

In another embodiment, this invention provides a process for preparing compound iv comprising subjecting compound iii under conditions to provide compound iv. Accordingly, in step 2, compound iii is made to undergo an intramolecular Heck type cyclization, preferably in an inert solvent, in the presence of 100-130 mole %, with respect to compound iii, of a Pd(II) salt, and an oxidant such as a silver (I). A reducing agent, such as a borohydride is used to reductively workup the reaction mixture to provide compound iv. The reaction is carried out at 30-90° C. for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, NMR spectroscopy, and the likes. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the products may be used for a subsequent reaction without further purification.

In another embodiment, this invention provides a process for preparing compound vi comprising contacting compound v with R^4 -M, wherein R^4 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_6 alkynyl, optionally substituted with a protected form of amino or hydroxy, and M is lithium or magnesium halide, under conditions to provide compound vi. Accordingly, in step 3, compound v, which is compound iv wherein $C(R^4)_2$ is a keto group, and which is readily obtained from compound iv, where $C(R^4)_2$ is a cyclic ketal or thioether by deprotection, is reacted with an R^4 anion equivalent, R^4 -M, wherein M is lithium, a magnesium halide, and the like. The reaction is carried out, preferably with about a 10 fold excess of the R^4 -M in an inert solvent such as ether or tetrahydrofuran at a temperature of -5° C. to 15° C. for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, 1H -nuclear magnetic resonance (NMR) spectroscopy, and the likes. After aqueous work-up using, for example, water, aqueous NH_4Cl or aqueous tartrate, the product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the products may be used for a subsequent reaction without further purification.

In another embodiment, this invention provides a process for preparing compound vii comprising subjecting compound vi under conditions to provide compound vii. Accordingly, in step 4, compound vi is dehydrated, preferably using an acid such as a sulfonic acid to provide compound vii. The dehydration is carried out in an inert solvent, preferably at a temperature where the solvent refluxes, for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as

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thin layer chromatography, NMR spectroscopy, and the likes. Various solvents useful for this purpose is well known in the art and will be apparent to the skilled artisan upon reading this disclosure. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the products may be used for a subsequent reaction without further purification.

In another embodiment, this invention provides a process for preparing compound viii comprising subjecting compound vii under conditions to provide compound viii. Accordingly, in step 5, the amide carbonyl of compound vii is reduced to a $-\text{CH}_2-$ moiety by reacting with a borohydride, optionally activated with a Lewis acid, such as BF_3 etherate, or with an aluminum hydride. The reaction is performed in an inert solvent, preferably, an ether or tetrahydrofuran at a temperature of $0-50^\circ\text{C}$. or in a refluxing solvent. The reaction is carried out for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, NMR spectroscopy, and the likes. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the products may be used for a subsequent reaction without further purification.

In another embodiment, this invention provides a process for preparing compound ix comprising subjecting compound viii under conditions to provide compound ix. Accordingly, in step 6, compound viii is hydrogenated to provide compound viii. The hydrogenation is carried out using Pd or Pt or their oxides or hydroxides adsorbed on a solid support such as carbon, alumina, and the like, preferably in an amount less than 100 mole % with respect to compound viii, and hydrogen. The hydrogenation is carried out in an inert solvent, such as an alcohol, ethyl acetate, or an ether, at $15-30^\circ\text{C}$. for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, NMR spectroscopy, and the likes. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation.

In certain process embodiments, $\text{C}(\text{R}^4)_2$ is a keto ($\text{C}=\text{O}$) group. In other process embodiments, for compounds i and iii, $\text{C}(\text{R}^4)_2$ is cyclic ketal or thioketal. In other process embodiments, R^5 is NH. In certain other process embodiments, R^5 is O. In certain other process embodiments, for compounds, vi-ix, R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, optionally substituted with 1-3 substituents, as provided herein, or their protected forms that will be apparent to the skilled artisan.

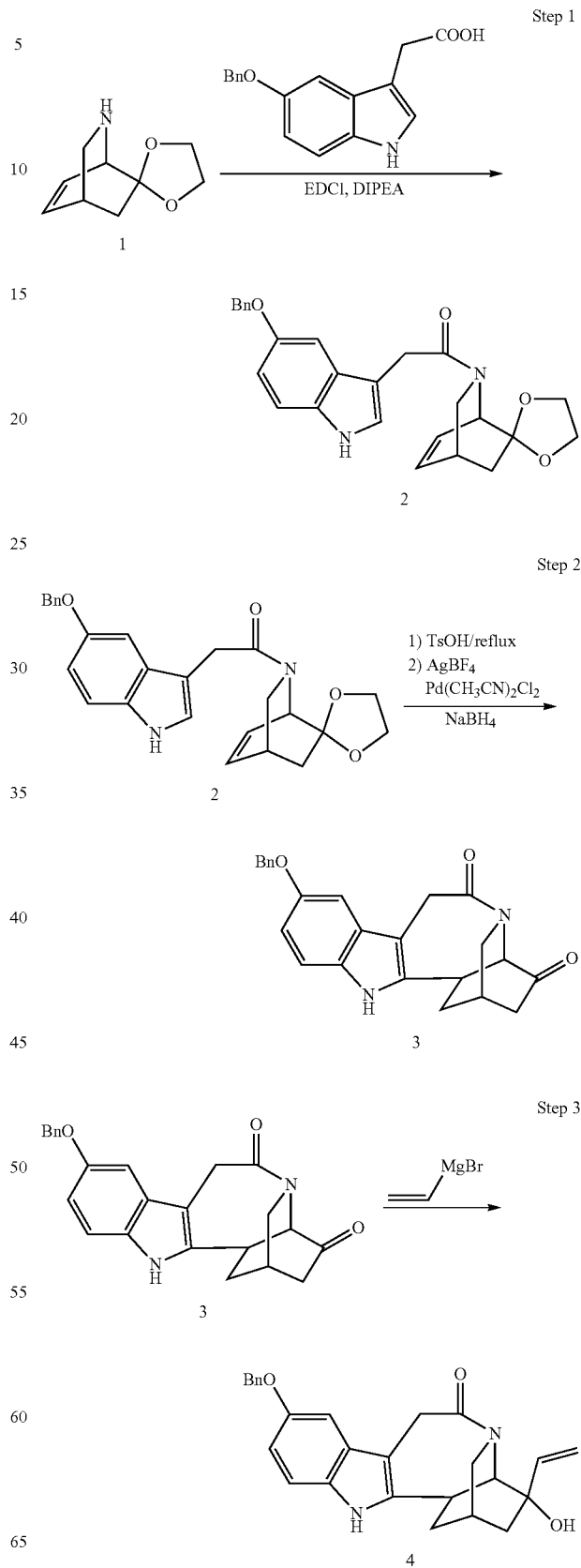
It will be apparent to the skilled artisan upon reading this disclosure that the sequence of steps shown in Scheme 1, are preferred illustrative sequences, and can be altered in manners apparent to the skilled artisan to obtain the compounds provided herein.

Compounds of this invention where $\text{C}(\text{R}^4)_2$ is $\text{C}=\text{CR}^{48}\text{R}^{49}$ are conveniently prepared from the corresponding keto compound ($\text{C}(\text{R}^4)_2$ is keto) following Wittig and other related olefination procedures, as is well known to the skilled artisan.

In certain other of its process embodiments, this invention provides processes, preferably, enantioselective processes, for preparing (–) noribogaine, in a substantially enantiomerically pure form, as schematically illustrated below, where the reagents indicated are merely illustrative and are not limiting, as discussed in further detail below.

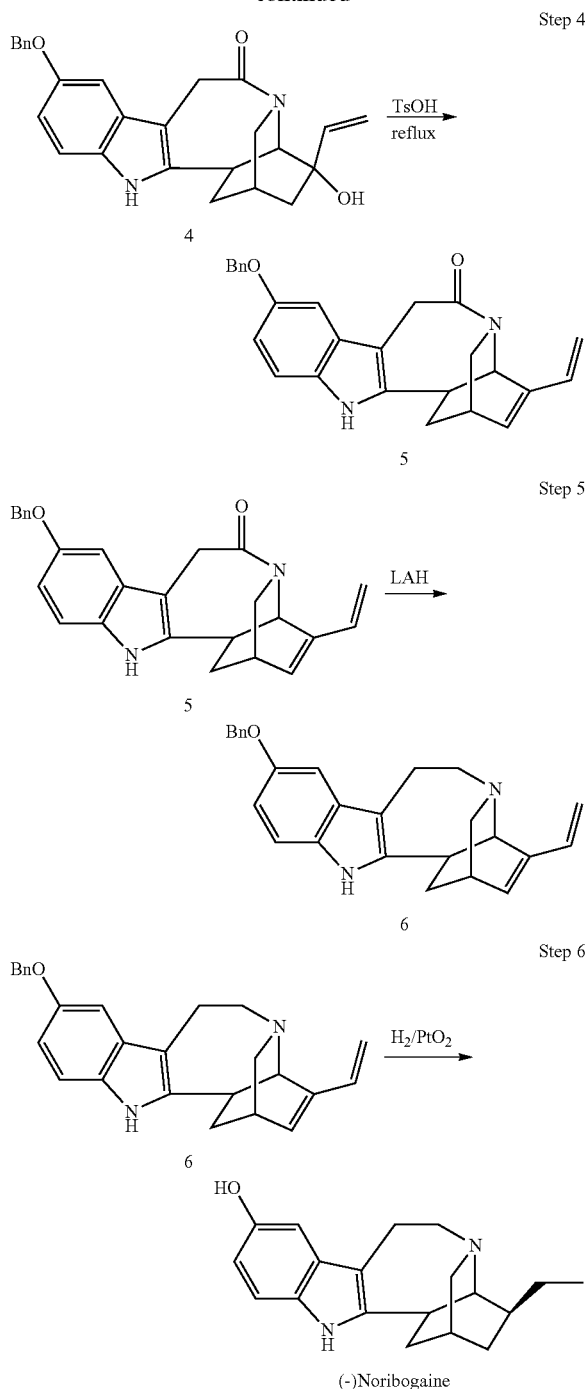
32

Scheme 2



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-continued



In one embodiment, this invention provides a process for preparing compound 2 comprising contacting compound 1 with 5-benzyloxyindoleacetic acid under conditions to provide compound 2. Thus, in step 1, Compound 1 is coupled with the benzyloxy substituted indole acetic acid to provide compound 2. The coupling is performed preferably in an inert solvent, such as a chlorinated solvent such as dichloromethane, or in tetrahydrofuran, or acetonitrile, in the presence of an amide or ester coupling reagent. Various such coupling agents such as carbodiimides or HBTU or HATU, and their immobilized derivatives are well known in the art and available commercially, for example, from Sigma-Aldrich

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Co. In a preferred embodiment, the coupling is performed in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and a hindered base, such as diisopropylethylamine (DIPEA). In one embodiment, The reaction is carried out at 0-50° C. for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, NMR spectroscopy, and the likes. FIG. 3 demonstrates the ¹H-NMR spectrum of compound 2. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the product may be used for a subsequent reaction without further purification.

In another embodiment, this invention provides a process for preparing compound 3 comprising subjecting compound 2 under conditions to provide compound 3. Thus, in step 2, compound 2 is deprotected by reacting with an aqueous acid. Various mineral acids such as sulfuric acid or hydrochloric acid, and sulfonic acids, such as toluene sulfonic acid are useful as the acid. Following the deprotection, the deprotected compound is subjected to an intramolecular Heck type cyclization. Various art known palladium reagents, such as palladium chloride and complexes thereof (such as the bis acetonitrile complex) are useful as the cyclization reagent, used in 100-130 mole % with respect to compound 2, further in presence of an oxidant, such as a Ag(I) salt. Reductive workup, employing a borohydride was demonstrated to provide compound 3 (see, FIG. 1). The reaction is carried out in an inert solvent, such as acetonitrile, alcohols, acetic acid, and mixtures thereof, at 30-90° C., preferably at 60-80° C. for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, NMR spectroscopy, and the likes. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the product may be used for a subsequent reaction without further purification.

In another embodiment, this invention provides a process for preparing compound 4 comprising contacting compound 3 with an ethyl anion equivalent under conditions to provide compound 4. As used herein, an ethyl anion equivalent is an anion that after this reaction is easily converted to an ethyl group. Thus, in step 3, compound 3 is reacted with an ethyl anion equivalent, such as, vinyl magnesium bromide (in a 10 fold mole/mole excess with respect to compound 3), in ether, tetrahydrofuran or a mixture thereof to provide after aqueous work up, compound 4. The reaction is carried out for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, NMR spectroscopy, and the likes. The product can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization, and precipitation, or the product may be used for a subsequent reaction without further purification.

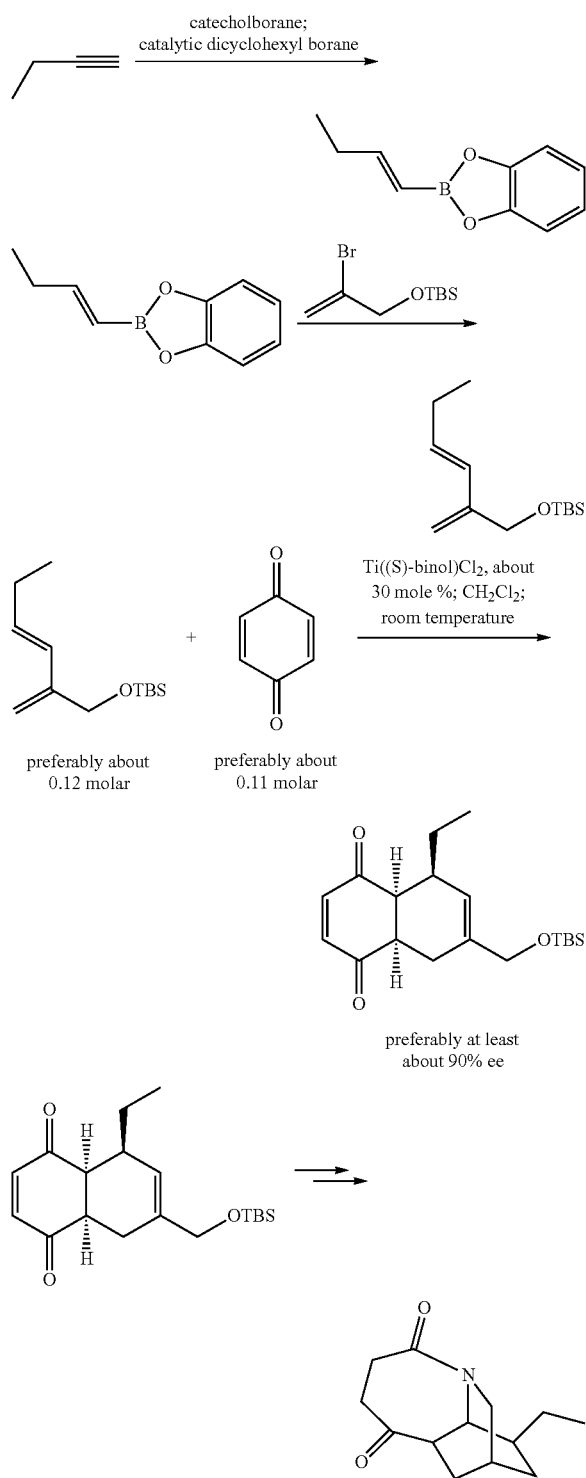
In another embodiment, this invention provides a process for preparing compound 5 comprising subjecting compound 4 under conditions to provide compound 5. Thus, in step 4, compound 4 is dehydrated to provide compound 5. The dehydration is performed preferably using an acid such as a sulfonic acid such as toluene sulfonic acid to provide compound vii. The dehydration is carried out in an inert solvent, preferably at a temperature where the solvent refluxes, for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, NMR spectroscopy, and the

Conjugate addition of vinyl magnesium bromide, oxazolidine ring cleavage, and keto group protection converts compound 7 to compound 8. Compound 8 is oxidized using NMO and tetrapropylammonium perruthenate to provides compound 9. Olefination of 9 yields the 1,5 divinyl substrate piperidine (10). Grubbs ring closing metathesis cyclization of 10 using the well known and commercially available Grubbs' or Schrock catalysts yields optically active (11) which is the carbonyl group and N-protected derivative compound 6. Deprotection of compound 11 with methyl lithium was demonstrated to provide compound 1. The ¹H-NMR of compound 1 is provided in FIG. 2. The reactions are carried out, preferably in an inert solvent that will be apparent to the skilled artisan upon reading this disclosure, and at temperatures that will also be apparent to the skilled artisan upon reading this disclosure. The reactions are performed for a period of time sufficient to provide a substantial amount of the product, which can be ascertained by using routine methods such as thin layer chromatography, ¹H-nuclear magnetic resonance (NMR) spectroscopy, and the likes. The products can be isolated and optionally purified using standard purification techniques, such as liquid chromatography, crystallization,

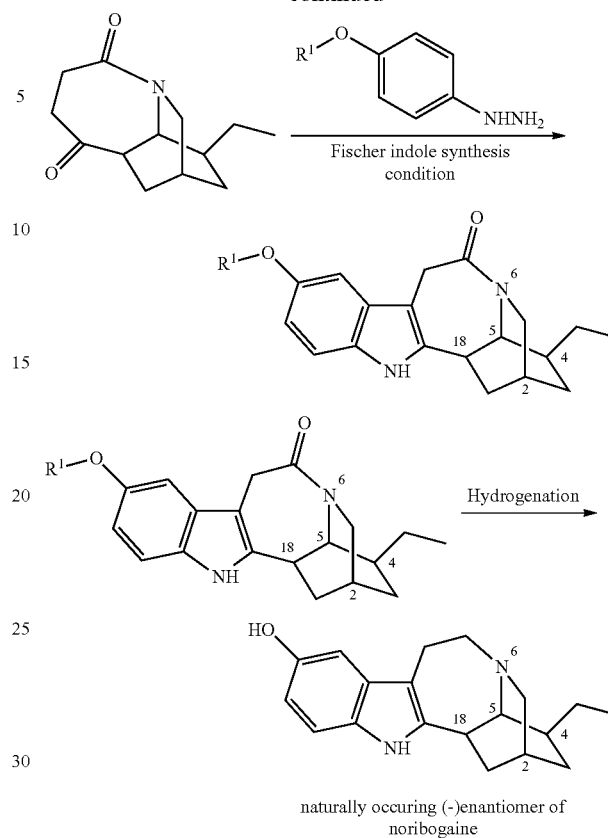
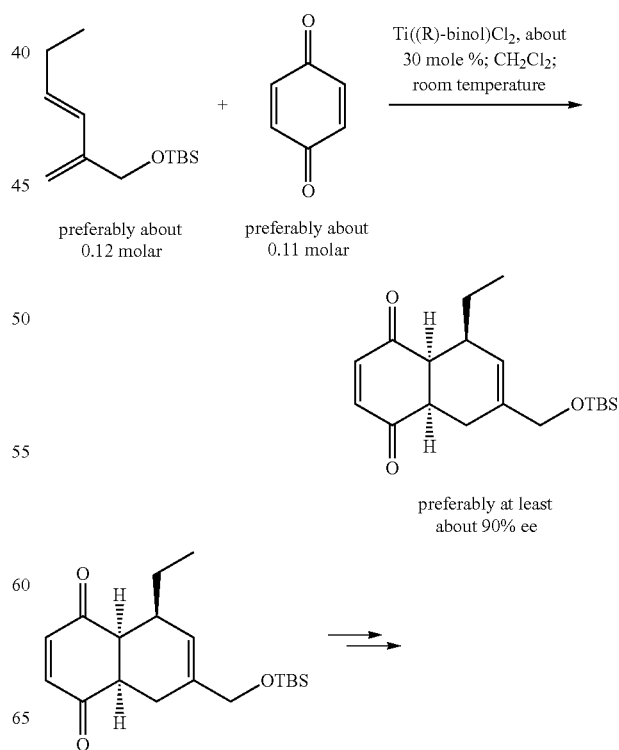
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precipitation, and distillation under reduced pressure, or the products may be used for a subsequent reaction without further purification.

Other processes of this invention for preparing (–) and (+) noribogaine are schematically illustrated and described below.

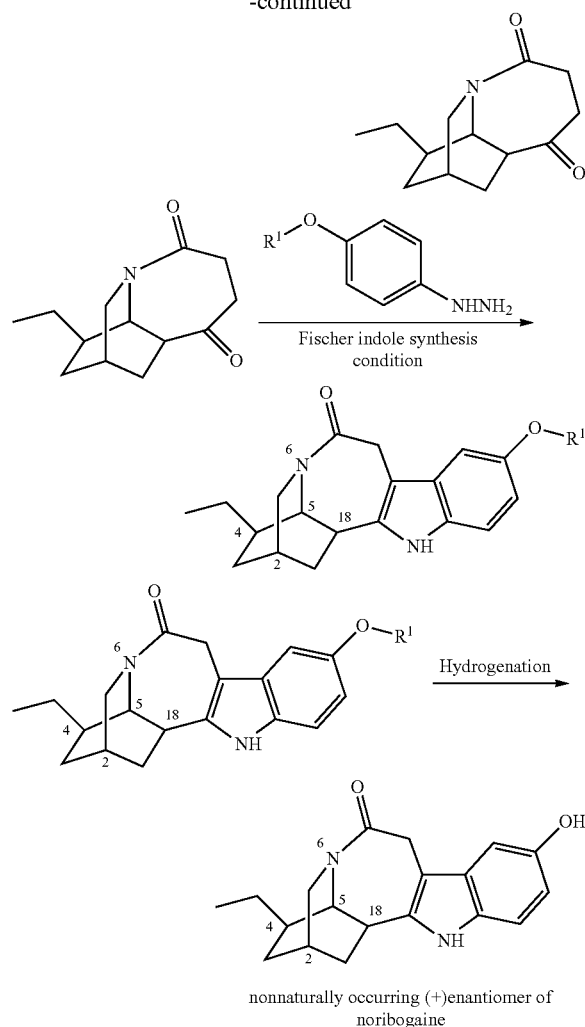
Scheme 4**38**

-continued

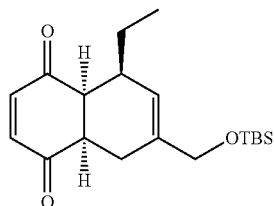
**Scheme 5**

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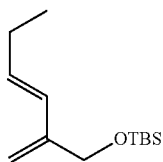
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Thus, in one embodiment, this invention provides a process for preparing a compound of formula:

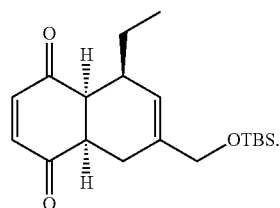


comprising contacting benzoquinone with a diene compound of formula:



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and a $\text{Ti}((S)\text{-binol})\text{Cl}_2$ catalyst under conditions to provide the compound of formula:



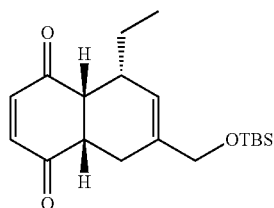
It is contemplated that other silicon protecting group such as TIPS, TBDMS, or triphenyl silyl can be reasonably used in place of TBS. Benzoquinone is combined with, e.g., at least an equimolar amount of the diene in an inert chlorinated solvent in presence of a catalytic amount, preferably 20%-35% molar amount, still more preferably, 25%-30% molar amount with respect to benzoquinone, of $\text{Ti}((S)\text{-binol})\text{Cl}_2$. The concentration of the reactants and the catalyst in the reaction solvent are as follows: benzoquinone, 0.05-0.2 molar, preferably 0.09-0.13 molar, still more preferably 0.11 molar; diene, 0.05-0.2 molar, preferably 0.1-0.14 molar, still more preferably 0.12 molar; and the catalyst, 0.01-0.1 molar, preferably 0.02-0.06 molar, still more preferably 0.03 molar. The reaction is performed at room temperature for a period of time sufficient to effect a substantial completion of the reaction.

While performing the above reaction under the conditions described, it was surprisingly observed that the desired enantiomer was obtained in 96% ee. Such a high ee allows the reaction to be used for manufacturing highly enantiomerically pure noribogaine suitable for human administration at reasonable manufacturing costs. The ee obtained for this reaction surpasses the 87% ee reported by White et al., *Helv. Chim. Acta*, Vol. 85 (2002), 4306-4327 (White), and incorporated herein in its entirety by reference. In White, despite optimization, a higher ee was not obtained. See, White at page 4314. An 87% ee corresponds to 93.5% of the major enantiomer. A process with 87% ee is undesirable from a manufacturing standpoint because it lowers chemical yield of the desired enantiomer, and adds one or more extra steps to separate the desired enantiomer from the undesired enantiomer. However, it is well known that when the ee excess is already around 87% after substantial optimization, it is challenging to improve it further. Under the conditions White reported, toluene was used as the reaction solvent and the following concentrations of the reactants and the catalyst were used: benzoquinone (0.83 molar), diene (0.97 molar), and catalyst (0.25 molar). Furthermore, according to White, 4 angstrom molecular sieves used during in situ preparation of the catalyst was removed by centrifugation.

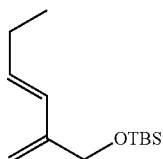
Therefore it was surprising that in the above reaction, when dichloromethane was used in place of toluene, the concentrations of the reactants and the catalyst were reduced by about 7 fold, and the molecular sieves used for preparing the catalyst were filtered off instead of being removed by centrifugation, the ee of the diene obtained increased to 96%. Or in other words, the reaction produced 98% of the desired enantiomer.

In another embodiment, this invention provides a process for preparing a compound of formula:

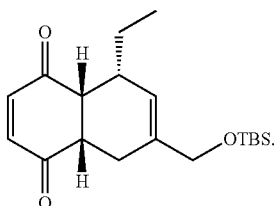
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comprising contacting benzoquinone with a diene compound of formula:

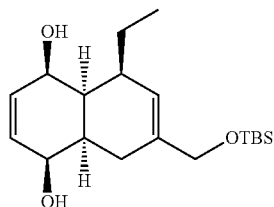


and a $\text{Ti}((R)\text{-binol})\text{Cl}_2$ catalyst under Diels Alder reaction conditions to provide the compound of formula:

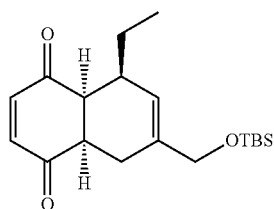


It is contemplated that another silicon protecting group be reasonably used in place of OTBS. Preferred reaction conditions for this reaction are the same as those described above for the Diels Alder reaction using a $\text{Ti}((S)\text{-binol})\text{Cl}_2$ catalyst. $\text{Ti}((R)\text{-binol})\text{Cl}_2$ or $\text{Ti}((S)\text{-binol})\text{Cl}_2$ is preferably prepared in situ by reacting (R) or (S)-binol with $\text{Ti}(\text{—OCHMe}_2)_2\text{Cl}_2$.

In another embodiment, this invention provides a process for preparing a compound of formula:



comprising contacting the compound of formula:

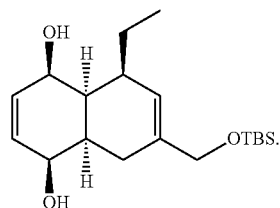


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with a reducing agent under conditions to provide the compound of formula:

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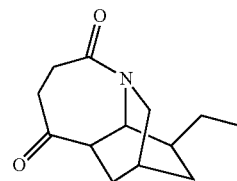


In a preferred embodiment, the reducing agent is diisobutylaluminum hydride.

In another embodiment, this invention provides a process for preparing a compound of formula:

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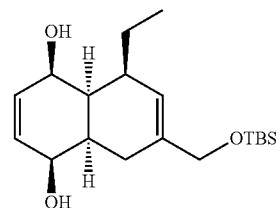


comprising the steps of:

(i) contacting the compound of formula

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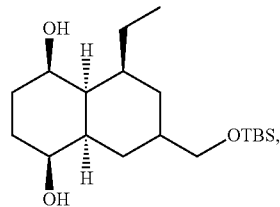
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under hydrogenation conditions to provide a compound of formula

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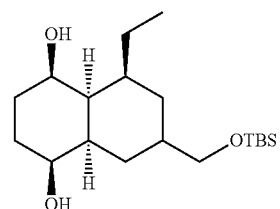


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(ii) contacting the compound of formula:

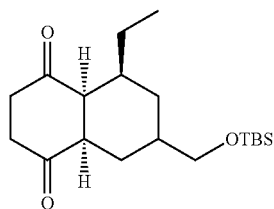
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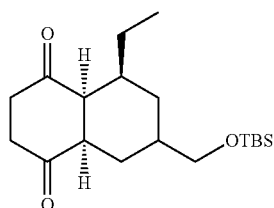


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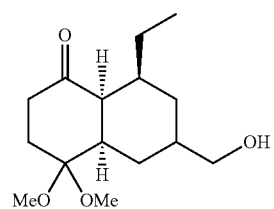
with an oxidizing agent under conditions to provide a compound of formula:



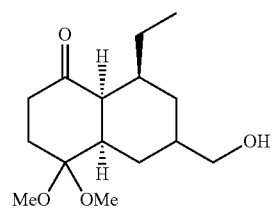
(iii) contacting the compound of formula:



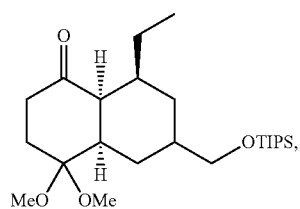
with methanol and pyridinium para toluene sulfonate to provide a compound of formula:



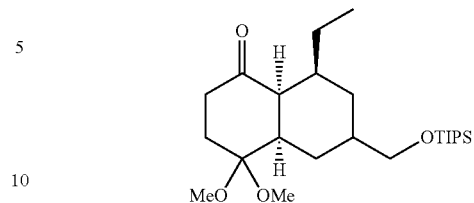
(iv) contacting the compound of formula:



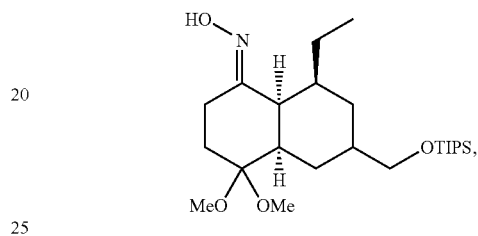
with triisopropyl silyl chloride and imidazole to provide the compound of formula:

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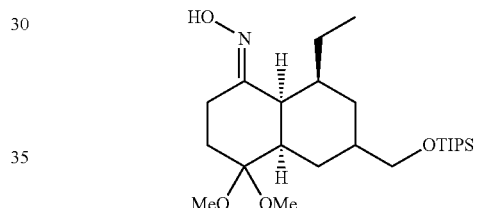
(v) contacting the compound of formula:



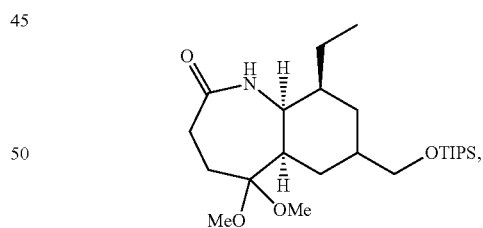
with a salt of NH_2OH and a base to provide the compound of formula:



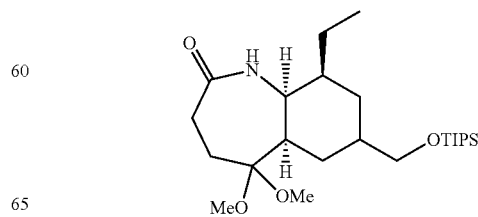
(vi) contacting the compound of formula



with $\text{R}^s\text{SO}_2\text{Cl}$ wherein R^s is alkyl, fluoroalkyl, aryl, or aryl substituted with an alkyl or a halogen group, a base, and optionally a nucleophilic catalyst such as 4-N,N-dialkylaminopyridine to provide a compound of formula:

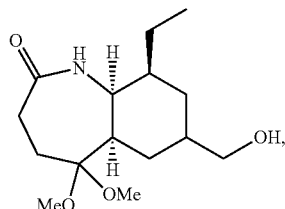


(vii) contacting the compound of formula:

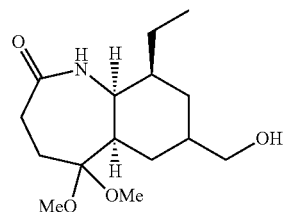


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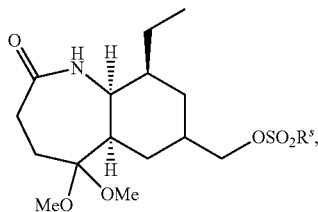
with fluoride anion to provide the compound of formula:



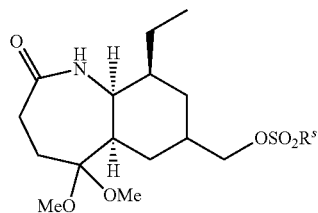
(viii) contacting the compound of formula:



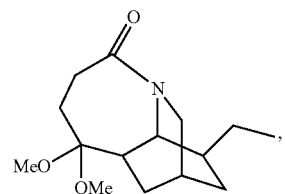
with R^sSO_2Cl wherein R^s is alkyl, fluoroalkyl, aryl, or aryl substituted with an alkyl or a halogen group, a base, and optionally a 4-N,N-dialkylaminopyridine to provide a compound of formula:



(ix) contacting the compound of formula:

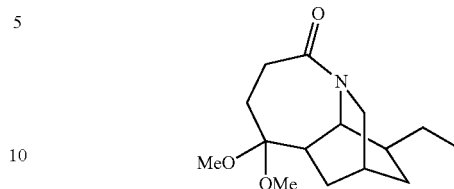


with a non nucleophilic base to provide a compound of formula:

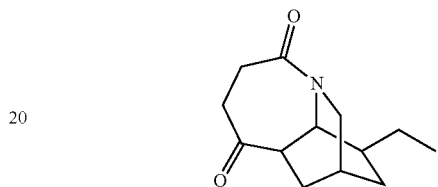


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and
(x) contacting the compound of formula:



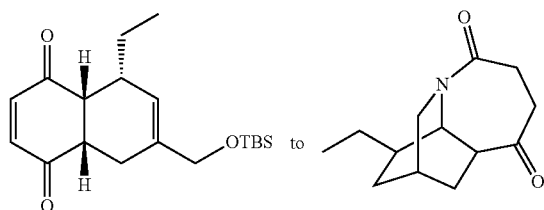
with an acid to provide the compound of formula:



Steps (i) to (x) can be performed substantially according to the methods described in White, supra. In step (i), the hydrogenation is performed preferably employing a catalyst such as Rh/Al_2O_3 and hydrogen, which catalyst does not produce substantial amounts of the hydrogenolyzed product. Upon hydrogenolysis, the allylic hydroxy group(s) can be replaced by hydrogen atom(s). A variety of oxidizing agents can be employed for step (ii) such as for example pyridinium dichromate, pyridinium chlorochromate, and the like. Those oxidizing agents are preferred that would not convert the tributylsilyloxy (OTBS) group to an $-OH$ group. The selective ketalization of the less hindered ketone in step (iii) is performed using a mild acid catalyst such as pyridinium para toluene sulfonate (PPTS). In step (v), a salt of NH_2OH is reacted with the ketone and a base to provide the oxime. A variety of bases may be employed, including without limitation, acetates, preferably alkali metal acetates, alkali, and nitrogen containing bases such as pyridine, triethyl amine and the like. In step (vi), a variety of sulfonyl chlorides may be used, including without limitation para toluene sulfonyl chloride. In step (vi), a variety of bases may be employed, including without limitation, alkali and nitrogen containing bases such as pyridine, triethyl amine and the like. Preferred nucleophilic catalysts include 4-N,N-dimethylaminopyridine and 4-pyrrolidinopyridine. In step (vii) a variety of fluoride sources may be used including tertiary alkyl ammonium fluorides, such as tetrabutylammonium fluoride. In step (viii), a variety of bases may be employed, including without limitation, alkali and nitrogen containing bases such as pyridine, triethyl amine and the like. Preferred nucleophilic catalysts include 4-N,N-dimethylaminopyridine and 4-pyrrolidinopyridine. In step (ix), preferred non-nucleophilic bases used include, hydrides such as sodium, potassium and calcium hydrides. In step (x), a variety of acids can be used to convert the dimethyl ketal to the ketone. These reactions are carried out in solvents that are inert under the reaction conditions. The reactions are carried out for a time sufficient to provide substantial amount of the desired product. The reactions are monitored by thin layer chromatography. Depending on the amount of impurity present, a product may be separated by column chromatography, crystallization, or such other techniques well known to the skilled artisan, or the reaction product may be used without further purification in the next step.

In another embodiment, this invention provides a process for converting:

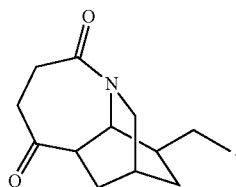
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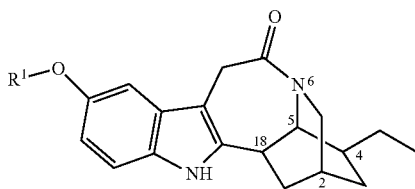
following the process provided hereinabove for synthesizing:



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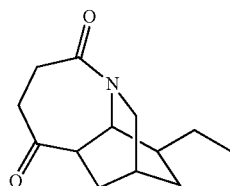
In another embodiment, this invention provides a process for preparing a compound of formula:



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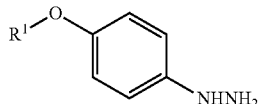
comprising contacting a ketoamide compound of formula:



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with a substituted phenyl hydrazine of formula:



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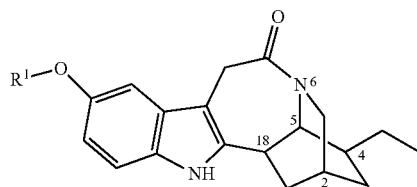
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or a salt thereof, wherein R¹ is C₁-C₄ alkyl optionally substituted with 1-3 phenyl or substituted phenyl groups, wherein the substituted phenyl is substituted with 1-3 C₁-C₄ alkyl or C₁-C₄ alkoxy groups, under Fischer indole synthesis conditions to provide the keto ibogaine derivative of formula:

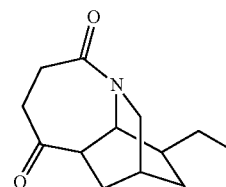
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In another embodiment, R¹ is methyl. In another embodiment, R¹ is a methyl group substituted with 1-3, preferably 1-2, more preferably 1 phenyl group, which phenyl group is optionally substituted with 1-3 C₁-C₄ alkyl or C₁-C₄ alkoxy groups. In another embodiment, R¹ is benzyl. When R¹ is methyl, it is preferred to not use a boron based Lewis acid, such as BF₃ etherate, for this transformation.

In another embodiment, the ketoamide compound is present at least 80%, preferably at least 90%, more preferably at least 95%, or still more preferably at least 98% as the (5aR,7R,9S,9aS)-9-ethyl-3,4,5a,6,7,8,9,9a-octahydro-1,7-methano-1H-benz[b]azepine-2,5-dione enantiomer:



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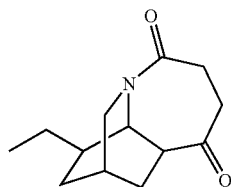
In other words, the ketoamide compound contains, at least 60%, preferably at least 80%, more preferably at least 90%, or still more preferably at least 96% ee of the (5aR,7R,9S,9aS)-9-ethyl-3,4,5a,6,7,8,9,9a-octahydro-1,7-methano-1H-benz[b]azepine-2,5-dione enantiomer.

In another embodiment, the keto ibogaine derivative is present at least 80%, preferably at least 90%, more preferably at least 95%, or still more preferably at least 98% as the 2(R), 4(S), 5(S), 6(S) and 18(R) enantiomer.

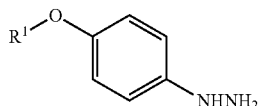
It is surprising that a substituted hydrazine containing an electron donating 4-alkoxy substituent effectively provides the tricyclic indole under Fischer indole synthesis conditions. The ketoamide compound is combined with at least an equimolar amount of the substituted phenylhydrazine or a salt thereof, in the presence of an acid or a mixture of acids. Suitable acids include carboxylic Bronsted acids such as acetic acid and Lewis acids such as BF₃ and its solvates such as etherates. The reaction is performed at 40° C.-60° C., and may optionally be warmed up to 70° C.-90° C., for a period of time sufficient to effect a substantial completion of the reaction. Suitable solvent include acetic acid, propionic acid and the like. Suitable salts of the substituted phenylhydrazine include salts of mineral acids, such as HCl.

In another embodiment, this invention provides a method of synthesis comprising contacting a ketoamide compound of formula:

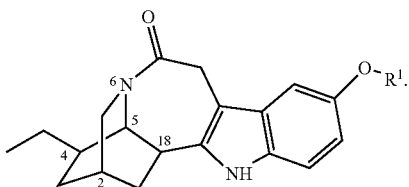
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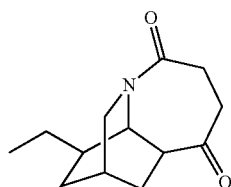
with a substituted phenyl hydrazine of formula:



or a salt thereof, wherein R¹ is C₁-C₄ alkyl optionally substituted with 1-3 phenyl or substituted phenyl groups, wherein the substituted phenyl is substituted with 1-3 C₁-C₄ alkyl or C₁-C₄ alkoxy groups, under Fischer indole synthesis conditions to provide a keto ibogaine derivative of formula:

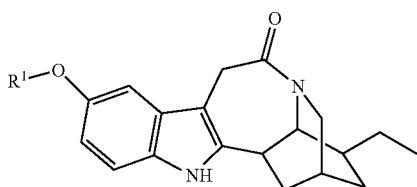


In another embodiment, the ketoamide compound is present at least 80%, preferably at least 90%, more preferably at least 95%, or still more preferably at least 98% as the (5a*S*,7*S*,9*R*,9a*R*)-9-ethyl-3,4,5a,6,7,8,9,9a-octahydro-1,7-methano-1*H*-benz[*b*]azepine-2,5-dione enantiomer:



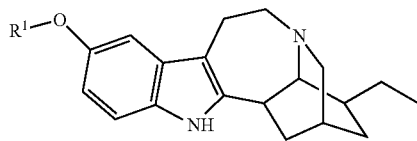
In another embodiment, the keto ibogaine derivative is present at least 80%, preferably at least 90%, more preferably at least 95%, or still more preferably at least 98% as the 2(*S*), 4(*R*), 5(*R*), 6(*R*) and 18(*S*) enantiomer.

In another embodiment, the process further comprises subjecting the keto ibogaine derivative:



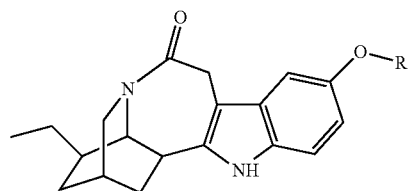
under amide reduction conditions to provide ibogaine or the derivative thereof of formula:

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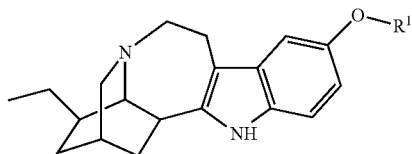


The keto ibogaine derivative is contacted with at least an equimolar, preferably 4-6 molar excess of a borohydride, preferably NaBH₄ and a Lewis acid, preferably, BF₃ etherate, in an inert solvent such as tetrahydrofuran. The reaction is performed initially at 0° C. and then at room temperature for a period of time sufficient to effect a substantial completion of the reaction.

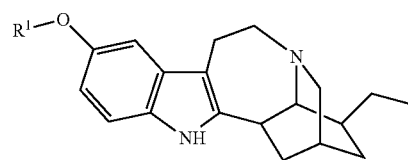
In another embodiment, the process further comprises subjecting the keto ibogaine derivative:



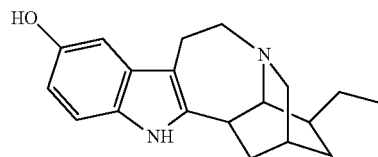
under amide reduction conditions to provide ibogaine or a derivative thereof of formula:



In another embodiment, the process further comprises deprotecting the compound of formula:



under deprotection conditions to provide naturally occurring (-) noribogaine:

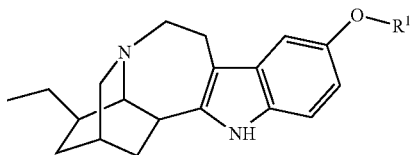


In another embodiment, the noribogaine obtained is present at least 80%, preferably at least 90%, more preferably at least 95%, or still more preferably at least 98% as the (-) or naturally occurring 2(*R*), 4(*S*), 5(*S*), 6(*S*) and 18(*R*) enantiomer of noribogaine. In another embodiment, R¹ is C₁-C₄

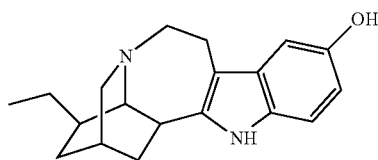
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alkyl, and the deprotection is performed by using BBr_3 in an inert solvent under conditions well known to the skilled artisan. In another embodiment, R^1 is benzyl and the deprotection is performed by using hydrogenolysis or catalytic hydrogenation conditions.

In another embodiment, the process further comprises deprotecting the compound of formula:



under deprotection conditions to provide noribogaine:



or a salt thereof.

In another embodiment, the noribogaine obtained is present at least 80%, preferably at least 90%, more preferably at least 95%, or still more preferably at least 98% as the (+) or nonnatural 2(S), 4(R), 5(R), 6(R) and 18(S) enantiomer of noribogaine.

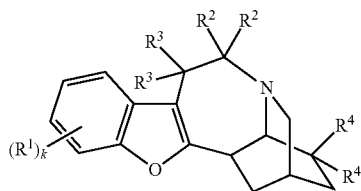
In another aspect, this invention provides (–) noribogaine and (+)noribogaine, and intermediates thereto, preferably in substantially enantiomerically pure forms, prepared according to the processes provided herein.

UTILITY

The indole isoquinuclidene derivative (–) noribogaine has utility in the treatment of drug dependency and as an analgesic. See U.S. Pat. Nos. 6,348,456 7,220,737, *supra*. The indole and benzofuran fused isoquinuclidene derivatives provided and (+) noribogaine herein have utility to test their interaction with the opioid receptors to better understand the mechanism of (–) noribogaine's analgesic action. The novel compounds provided herein also have utility as intermediates to synthetic noribogaine or as compounds having activity in drug dependency or as analgesics.

The invention claimed is:

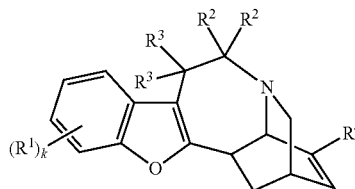
1. A compound of Formula (I-i) or (VI-i):



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-continued

(VI-i)



or a salt or enantiomer thereof wherein

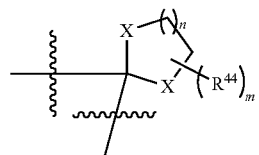
k is 1, 2, or 3;

each R^1 is independently selected from the group consisting of hydrogen, halo, amino, hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, cyano, nitro, —N_3 , and $\text{—CO}_2\text{H}$ or an ester thereof, wherein the alkyl, alkoxy, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, —N_3 , phenyl optionally substituted with 1-3 substituents selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_1\text{-C}_6$ alkoxy, and $\text{—CO}_2\text{H}$ or an ester thereof;

R^2 is hydrogen or $\text{C}(\text{R}^2)_2$ is a keto group;

R^3 is selected from the group consisting of hydrogen, halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, halo, amino, hydroxy, cyano, nitro, —N_3 , and $\text{—CO}_2\text{H}$ or an ester thereof;

each R^4 independently is selected from the group consisting of hydrogen, hydroxy, —SR^{41} , —OR^{42} , $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, and $\text{C}_2\text{-C}_6$ alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of, halo, $\text{C}_1\text{-C}_6$ alkoxy, amino, hydroxy, cyano, nitro, —NHCOCH_3 , and —N_3 , or the 2 R^4 groups together with the carbon atom to which they are bonded to form a keto (C=O) group, a Schiff base ($=\text{NR}^{43}$), a vinylidene moiety of formula $=\text{CR}^{48}\text{R}^{49}$, or form a cyclic ketal or thioketal, which cyclic ketal or thioketal is of formula:



each R^{41} is independently selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl optionally substituted with 1-3 substituents selected from the group consisting of $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_{10}$ heteroaryl, $\text{C}_3\text{-C}_8$ heterocyclyl, halo, amino, —N_3 , hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, silyl, nitro, cyano, and CO_2H or an ester thereof, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_2\text{-C}_{10}$ heteroaryl, $\text{C}_3\text{-C}_8$ cycloalkyl, and $\text{C}_3\text{-C}_8$ heterocyclyl;

each R^{42} is independently selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl optionally substituted with 1-3 substituents selected from the group consisting of $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_{10}$ heteroaryl, $\text{C}_3\text{-C}_8$ heterocyclyl, halo, amino, —N_3 , hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, silyl, nitro, cyano, and CO_2H or an ester thereof, $\text{C}_2\text{-C}_6$ alkenyl, and $\text{C}_2\text{-C}_6$ alkynyl;

where X in both occurrences is either oxygen or sulfur;

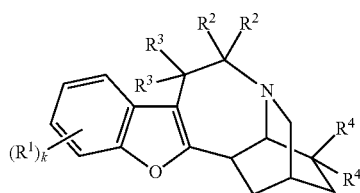
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m is 1, 2, 3, or 4;

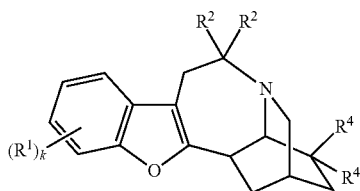
n is 1 or 2;

R⁴³ is selected from the group consisting of C₆-C₁₀ aryl and C₂-C₁₀ heteroaryl;R⁴⁴ is selected from the group consisting of C₁-C₆ alkyl and C₆-C₁₀ aryl;R⁴⁸ is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, and C₂-C₆ alkynyl, wherein the alkyl, alkenyl, or the alkynyl group is optionally substituted with 1-3 substituents selected from the group consisting of keto, C₁-C₆ alkoxy, amino, hydroxy, cyano, nitro, —NHCOCH₃, and —CO₂H or an ester thereof; andR⁴⁹ is hydrogen or C₁-C₆ alkyl.

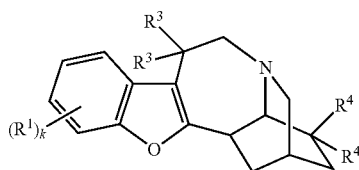
2. The compound of claim 1, of (IB):

wherein k and R¹, R², R³, and R⁴ are defined as in claim 1.

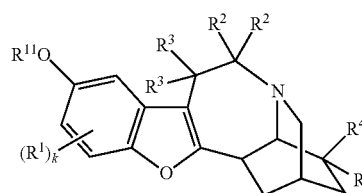
3. The compound of claim 1, of Formula (IIB):

wherein k and R¹, R², and R⁴ are defined as in claim 1.

4. The compound of claim 1, of Formula (IIIB):

wherein k and R¹, R³, and R⁴ are defined as in claim 1.**54**

5. A compound of Formula (IVB):

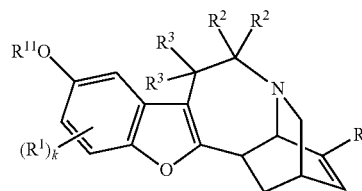
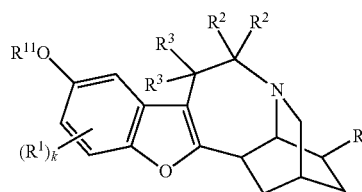


wherein R¹¹ is selected from the group consisting of hydrogen and C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of halo, amino, hydroxy, cyano, nitro, —N₃, and —CO₂H or an ester thereof, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of C₁-C₆ alkyl and C₁-C₆ alkoxy;

k is 1 or 2;

and R¹, R², R³, and R⁴ are defined as in claim 1.

6. A compound of Formula (IVD) or (VIB):



wherein R¹¹ is selected from the group consisting of hydrogen and C₁-C₆ alkyl optionally substituted with 1-3 substituents selected from the group consisting of halo, amino, hydroxy, cyano, nitro, —N₃, and —CO₂H or an ester thereof, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of C₁-C₆ alkyl and C₁-C₆ alkoxy;

k is 1 or 2;

and R¹, R², R³, and R⁴ are defined as in claim 1.

7. An isolated enantiomer of a compound of claim 1 in substantial enantiomeric excess.

* * * * *